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(54) Title: METHOD FOR MODULATING STEM CELL DIFFERENTIATION USING STEM LOOP RNA

(57) Abstract: This invention relates to a method to promote the differentiation of stem cells, typically embryonic stem cells, through the use of RNA interference, by the introduction of stem loop RNA into a cell.

Method for Modulating Stem Cell Differentiation Using Stem Loop RNA

The invention relates to a method to modulate stem cell differentiation comprising introducing stem loop containing RNA into a stem cell to ablate mRNA's which encode polypeptides which are involved in stem cell differentiation; stem loop RNA's ; and nucleic acid molecules and vectors encoding stem loop RNA's.

A number of techniques have been developed in recent years which purport to specifically ablate genes and/or gene products. For example, the use of anti-sense nucleic acid molecules to bind to and thereby block or inactivate target mRNA molecules is an effective means to inhibit the production of gene products. This is typically very effective in plants where anti-sense technology produces a number of striking phenotypic characteristics. However, antisense is variable leading to the need to screen many, sometimes hundreds of, transgenic organisms carrying one or more copies of an antisense transgene to ensure that the phenotype is indeed truly linked to the antisense transgene expression. Antisense techniques, not necessarily involving the production of stable transfectants, have been applied to cells in culture, with variable results.

In addition, the ability to be able to disrupt genes via homologous recombination has provided biologists with a crucial tool in defining developmental pathways in higher organisms. The use of mouse gene "knock out" strains has allowed the dissection of gene function and the probable function of human homologues to the deleted mouse genes, (Jordan and Zant, 1998).

A much more recent technique to specifically ablate gene function is through the introduction of double stranded RNA, also referred to as inhibitory RNA (RNAi), into a cell which results in the destruction of mRNA complementary to the sequence included in the RNAi molecule. The RNAi molecule comprises two complementary strands of RNA (a sense strand and an antisense strand) annealed to each other to

form a double stranded RNA molecule. The RNAi molecule is typically derived from exonic or coding sequence of the gene which is to be ablated.

Surprisingly, only a few molecules of RNAi are required to block gene expression which implies the mechanism is catalytic. The site of action appears to be nuclear as little if any RNAi is detectable in the cytoplasm of cells indicating that RNAi exerts its effect during mRNA synthesis or processing.

The exact mechanism of RNAi action is unknown although there are theories to explain this phenomenon. For example, all organisms have evolved protective mechanisms to limit the effects of exogenous gene expression. For example, a virus often causes deleterious effects on the organism it infects. Viral gene expression and/or replication therefore needs to be repressed. In addition, the rapid development of genetic transformation and the provision of transgenic plants and animals has led to the realisation that transgenes are also recognised as foreign nucleic acid and subjected to phenomena variously called quelling (Singer and Selker, 1995), gene silencing (Matzke and Matzke, 1998) , and co-suppression (Stam et. al., 2000).

Initial studies using RNAi used the nematode *Caenorhabditis elegans*. RNAi injected into the worm resulted in the disappearance of polypeptides corresponding to the gene sequences comprising the RNAi molecule(Montgomery et. al., 1998; Fire et. al., 1998). More recently the phenomenon of RNAi inhibition has been shown in a number of eukaryotes including, by example and not by way of limitation, plants, trypanosomes (Shi et. al., 2000) *Drosophila spp.* (Kennerdell and Carthew, 2000). Recent experiments have shown that RNAi may also function in higher eukaryotes. For example, it has been shown that RNAi can ablate *c-mos* in a mouse ooctye and also E-cadherin in a mouse preimplanation embryo (Wianny and Zernicka-Goetz, 2000).

The use of RNAi to ablate stem cell RNA is disclosed in our co-pending application, WO 02/16620, which is incorporated by reference.

During mammalian development those cells that form part of the embryo up until the formation of the blastocyst are said to be totipotent (e.g. each cell has the developmental potential to form a complete embryo and all the cells required to support the growth and development of said embryo). During the formation of the blastocyst, the cells that comprise the inner cell mass are said to be pluripotential (e.g. each cell has the developmental potential to form a variety of tissues).

Embryonic stem cells (ES cells, those with pluripotentiality) may be principally derived from two embryonic sources. Cells isolated from the inner cell mass are termed embryonic stem (ES) cells. In the laboratory mouse, similar cells can be derived from the culture of primordial germ cells isolated from the mesenteries or genital ridges of days 8.5-12.5 *post coitum* embryos. These would ultimately differentiate into germ cells and are referred to as embryonic germ cells (EG cells). Each of these types of pluripotential cell has a similar developmental potential with respect to differentiation into alternate cell types, but possible differences in behaviour (eg with respect to imprinting) have led to these cells to be distinguished from one another .

Typically ES/EG cell cultures have well defined characteristics. These include, but are not limited to;

i) maintenance in culture for at least 20 passages when maintained on fibroblast feeder layers;
ii) produce clusters of cells in culture referred to as embryoid bodies;
iii) ability to differentiate into multiple cell types in monolayer culture;
iv) can form embryo chimeras when mixed with an embryo host;
v) express ES/EG cell specific markers.

Until very recently, *in vitro* culture of human ES/EG cells was not possible. The first indication that conditions may be determined which could allow the establishment of

human ES/EG cells in culture is described in WO96/22362. The application describes cell lines and growth conditions which allow the continuous proliferation of primate ES cells which exhibit a range of characteristics or markers which are associated with stem cells having pluripotent characteristics.

More recently Thomson *et al* (1998) have published conditions in which human ES cells can be established in culture. The above characteristics shown by primate ES cells are also shown by the human ES cell lines. In addition the human cell lines show high levels of telomerase activity, a characteristic of cells which have the ability to divide continuously in culture in an undifferentiated state. Another group (Reubinoff et. al., 2000) have also reported the derivation of human ES cells from human blastocyts. Shamblott *et. al.*, 1998 have also described EG cell derivation. In Lake *et al* J Cell Science 2000, 113:555-66 and Rathjen et al J Cell Science 1999, 112: 601-12, ectodermal stem cells are disclosed. The above references are each both incorporated by reference in their entirety.

A feature of ES/EG cells is that, in the presence of fibroblast feeder layers, they retain the ability to divide in an undifferentiated state for several generations. If the feeder layers are removed then the cells differentiate. The differentiation is often to neurones or muscle cells but the exact mechanism by which this occurs and its control remain unsolved.

In addition to ES/EG cells a number of adult tissues contain cells with stem cell characteristics. Typically these cells, although retaining the ability to differentiate into different cell types, do not have the pluripotential characteristics of ES/EG cells. For example haemopoietic stem cells have the potential to form all the cells of the haemopoietic system (red blood cells, macrophages, basophils, eosinophils etc). All of nerve tissue, skin and muscle retain pools of cells with stem cell potential. Therefore, in addition to the use of embryonic stem cells in developmental biology, there are also adult stem cells which may also have utility with respect to determining the factors which govern cell differentiation. . Further recent studies have suggested

that some stem cells previously thought to be committed to a single fate, (e.g neurons) may indeed possess considerable pluripotentcy in certain situations. Neural stem cells have recently been shown to chimerise a mouse embryo and form a wide range of non-neural tissue (Clark et. al., 2000).

A further group of cells which have relevance to developmental biology are pluripotent embryonal carcinoma cells (EC cells) which are stem cells of teratocarcinomas, also referred to as teratomas, which are able to differentiate into all cell types found in these tumours. A teratocarcinoma also includes teratocarcinoma cells which do not have the full pluripotential characteristics of an EC cell but nevertheless can differentiate into a restricted number of differentiated tissues. These cells have many features in common with ES/EG cells. The most important of these features is the characteristic of pluripotentiality.

Teratomas contain a wide range of differentiated tissues, and have been known in humans for many hundreds of years. They typically occur as gonadal tumours of both men and women. The gonadal forms of these tumours are generally believed to originate from germ cells, and the extra gonadal forms, which typically have the same range of tissues, are thought to arise from germ cells that have migrated incorrectly during embryogenesis. Teratomas are therefore generally classed as germ cell tumours which encompasses a number of different types of cancer. These include seminoma, embryonal carcinoma, yolk sac carcinoma and choriocarcinoma.

The similar biology of EC cells with ES/EG cells has been exploited to study the developmental fates of cells and to identify cell markers commonly expressed in EC cells and ES/EG cells. For example, and not by way of limitation, the expression of specific cell surface markers SSEA-3 (+), SSEA-4 (+), TRA-1-60 (+), TRA-1-81 (+) (Shevinsky *et al* 1982; Kannagi *et al* 1983; Andrews *et al* 1984a; Thomson *et al* 1995); alkaline phosphatase (+) (Andrews et. al., 1996); and Oct 4 (Scholer et. al., 1989; Kraft et. al., 1996; Reubinoff et. al., 2000; Yeom et. al., 1996).

We have accumulated expression studies which identify a number of genes thought to be involved in determining the developmental fate of stem cells, particularly embryonic stem cells. By northern blotting we have identified the expression of human homologs of two signalling pathways believed to be critical in cell fate determination. Expression of ligands, receptors and downstream components of the Notch and Wingless signalling cascades have been elucidated. Using the model system NTERA2/D1 embryonal carcinoma cells we have recorded changes in the expression of some of these components as the cells differentiate. Bearing in mind the role these cascades play in embryonic development throughout the animal kingdom, these changes suggest a significant role for both the wingless and Notch signalling pathways in differentiation of stem cells. Furthermore the activity of some genes are required for differentiation to occur along specific pathways e.g. the myogenic gene MyoD1. Other genes have activity which inhibits cellular differentiation along particular pathways. We envisage regulation of stem cell differentiation to yield a specific cell type could be achieved by:

(i) inhibition of certain genes that normally promote differentiation along particular pathways; therefore promoting differentiation to alternate cell phenotypes;

(ii) inhibition of gene activity that prevents differentiation into particular cell types; and

(iii) a combination of (i) and (ii), see figure 1

In our co-pending application, WO02/16620, we introduce RNAi molecules homologous to genes encoding factors involved in stem cell differentiation. The differentiation of stem cells during embryogenesis, during tissue renewal in the adult and wound repair is under very stringent regulation; aberrations in this regulation underlie the formation of birth defects during development and are thought to underlie cancer formation in adults.

Generally, it is envisaged that stem cells are under both positive and negative regulation which allows a fine degree of control over the process of cell proliferation and cell differentiation: excess proliferation at the expense of cell differentiation can lead to the formation of an expanding mass of tissue – a cancer – whereas express differentiation at the expense of proliferation can lead to the loss of stem cells and production of too little differentiated tissue in the long term, and especially the loss of regenerative potential. Certain genes have already been identified to have a negative role in preventing stem cell differentiation. Such genes, like those of the Notch family, when mutated to acquire activity can inhibit differentiation; such mutant genes act as oncogenes. On the contrary, loss of function of such genes on their inhibition results in stem cell differentiation.

We propose to use EC cells has a model cell system to follow the effects of perturbations in stem cell differentiation. We further propose an alternative approach to introduce double stranded RNA molecules into stem cells to ablate mRNA's.

The invention relates to the provision of stem-loop RNA structures which can either be synthesised *in vitro* followed by transfection into a stem cell, or alternatively, synthesised *in vivo* by the stem cell from vectors which are provided with expression cassettes which include a DNA molecule which includes the coding sequence for the stem-loop RNA.

The DNA molecule encoding the stem-loop RNA is constructed in two parts, a first part which is derived from a gene the regulation of which is desired. The second part is provided with a DNA sequence which is complementary to the sequence of the first part. The cassette is typically under the control of a promoter which transcribes the DNA into RNA. The complementary nature of the first and second parts of the RNA molecule results in base pairing over at least part of the length of the RNA molecule to form a double stranded hairpin RNA structure or stem-loop. The first and second parts can be provided with a linker sequence.

According to a first aspect of the invention there is provided a method to modulate the differentiation state of a stem cell comprising:

(i) contacting a stem cell with at least one nucleic acid molecule comprising a sequence of a gene which mediates at least one step in the differentiation of said cell which nucleic acid molecule consists of a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length;

(ii) providing conditions conducive to the growth and differentiation of the cell treated in (i) above; and optionally

(iii) maintaining and/or storing the cell in a differentiated state.

In a preferred method of the invention said first and second parts are linked by at least one nucleotide base.

The provision of first and second sequences which are complementary to one another and which comprise at least part of the coding sequence of a gene involved in stem cell differentiation means that when the sequence is transcribed into RNA the complementarity between first and second sequences allows base pairing between first and second sequences to form a double stranded RNA structure, see Figure 1. The optional provision of a linking region bewteen first and second parts results in the formation of a so called "hair-pin" loop structure. The transcription of the nucleic acid provides many copies of the hair-pin loop RNA which effectively functions as a RNAi molecule.

In a preferred method of the invention said nucleic acid molecule is a stem loop RNA molecule. Alternatively, said nucleic acid molecule is a DNA molecule which encodes said stem loop RNA. Ideally said DNA molecule is a vector adapted for expression of said stem loop RNA.

The stem cell in (i) above may be a teratocarcinoma cell.

In a preferred method of the invention said conditions are *in vitro* cell culture conditions.

In a further preferred method of the invention said stem cell is selected from: pluripotent stem cells such as embryonic stem cell; embryonic germ cell and embryonal carcinoma cells; and lineage restricted stem cells such as, but not restricted to; haemopoietic stem cell; muscle stem cell; nerve stem cell; skin dermal sheath stem cell; liver stem cell; and teratocarcinoma cells.

It will be apparent that the method can provide stem cells of intermediate commitment. For example, embryonic stem cells could be programmed to differentiate into haemopoietic stems cells with a restricted commitment. Alternatively, differentiated cells or stem cells of intermediate commitment could be reprogrammed to a more pluripotential state from which other differentiated cell lineages can be derived.

In a further preferred method of the invention said stem cell is an embryonic stem cell or embryonic germ cell.

In a yet further preferred method of the invention said stem loop RNA molecule is derived from a gene which encodes a cell surface receptor expressed by a stem cell.

In a further preferred method of the invention said cell surface receptor is selected from: human Notch 1(hNotch 1); hNotch 2; hNotch 3; hNotch 4; TLE-1; TLE-2; TLE-3; TLE-4; TCF7; TCF7L1; TCFFL2; TCF3; TCF19; TCF1; mFringe; lFringe; rFringe; sel 1; Numb; Numblike; LNX; FZD1; FZD2; FZD3; FZD4; FZD5; FZD6; FZD7; FZD8; FZD9; FZD10; FRZB.

In an alternative preferred method of the invention said stem loop RNA molecule is derived from a gene which encodes a ligand.

Typically, a ligand is a polypeptide which binds to a cognate receptor to induce or inhibit an intracellular or intercellular response. Ligands may be soluble or membrane bound.

In a further alternative preferred method of the invention said ligand is selected from: D11-1; D113; D114; D1k-1; Jagged 1; Jagged 2; Wnt 1; Wnt 2; Wnt 2b; Wnt 3; Wnt 3a; Wnt5a; Wnt6; Wnt7a; Wnt7b; Wnt8a; Wnt8b; Wnt10b; Wnt11; Wnt14; Wnt15.

Alternatively, said gene is selected from: SFRP1; SFRP2; SFRP4; SFRP5; SK; DKK3; CER1; WIF-1; DVL1; DVL2; DVL3; DVL1L1;mFringe; lFringe; rFringe; sel1l; Numb; LNX Oct4;NeuroD1; NeuroD2; NeuroD3; Brachyury; MDFI.

In a further preferred method of the invention said stem loop RNA molecule is derived from at least one of the sequences identified in Table 4 or Figures 4-54.

In a yet futher preferred embodiment of the invention said sequence is derived from Oct 4. Preferably the Oct 4 sequence corresponds to nucleotide sequence about 610 to about 1032 of the Oct 4 sequence found in GenBank accession number NM_ 002701.

Many methods have been developed over the last 30 years to facilitate the introduction of nucleic acid into cells which are well known in the art and are applicable to the stem loop RNA structures disclosed herein or the vectors which encode said stem loop structures.

Methods to introduce nucleic acid into cells typically involve the use of chemical reagents, cationic lipids or physical methods. Chemical methods which facilitate the uptake of DNA by cells include the use of DEAE –Dextran (Vaheri and Pagano Science 175: p434) . DEAE-dextran is a negatively charged cation which associates

and introduces the nucleic acid into cells. Calcium phosphate is also a commonly used chemical agent which when co-precipitated with nucleic acid introduces the nucleic acid into cells (Graham et al Virology (1973) 52: p456).

The use of cationic lipids (eg liposomes (Felgner (1987) Proc.Natl.Acad.Sci USA, 84:p7413) has become a common method. The cationic head of the lipid associates with the negatively charged nucleic acid backbone to be introduced. The lipid/nucleic acid complex associates with the cell membrane and fuses with the cell to introduce the associated nucleic acid into the cell. Liposome mediated nucleic acid transfer has several advantages over existing methods. For example, cells which are recalcitrant to traditional chemical methods are more easily transfected using liposome mediated transfer.

More recently still, physical methods to introduce nucleic acid have become effective means to reproducibly transfect cells. Direct microinjection is one such method which can deliver nucleic acid directly to the nucleus of a cell (Capecchi (1980) Cell, 22:p479). This allows the analysis of single cell transfectants. So called "biolistic" methods physically shoot nucleic acid into cells and/or organelles using a particle gun (Neumann (1982) EMBO J, 1: p841). Electroporation is arguably the most popular method to transfect nucleic acid. The method involves the use of a high voltage electrical charge to momentarily permeabilise cell membranes making them permeable to macromolecular complexes.

More recently still a method termed immunoporation has become a recognised techinque for the introduction of nucleic acid into cells, see Bildirici *et al* Nature (2000) 405, p298. The technique involves the use of beads coated with an antibody to a specific receptor. The transfection mixture includes nucleic acid, antibody coated beads and cells expressing a specific cell surface receptor. The coated beads bind the cell surface receptor and when a shear force is applied to the cells the beads are stripped from the cell surface. During bead removal a transient hole is created through which nucleic acid and/or other biological molecules can enter. Transfection

efficiency of between 40-50% is achievable depending on the nucleic acid used. In addition the specificity of cell delivery of RNAi's can be enhanced by association or linkage of the RNAi to specific antibodies, ligands or receptors.

There are also a number of commercially available transfection kits which purport to provide high efficiency transfection of cells. A kit which is particularly preferred is sold under the tradename ExGen 500^{tm} by MBI Fermentas, Lithuania. ExGen is a polyethylenimine, non-liposomal transfection reagent.

According to a further aspect of the invention there is provided a stem loop RNA molecule derived from a coding sequence of at least one gene involved in stem cell differentiation comprising a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length.

In a preferred embodiment of the invention said first and second parts are linked by at least one nucleotide base. In a further preferred embodiment of the invention said first and second parts are linked by 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide bases. In a yet further preferred embodiment of the invention said linker is at least 10 nucleotide bases.

In a preferred embodiment said coding sequence is an exon.

Alternatively said RNA molecule is derived from intronic sequences or the 5' and/or 3' non-coding sequences which flank coding/exon sequences of genes which mediate stem cell differentiation.

In a further preferred embodiment of the invention the length of the RNA molecule is between 10 nucleotide bases (nb) –1000nb. More preferably still the length of the

RNA molecule is selected from 10nb; 20nb; 30nb; 40nb; 50nb; 60nb; 70nb; 80nb; 90nb. More preferably still said RNA molecule is 21nb in length.

In a further preferred embodiment of the invention said RNA molecule is 100nb; 200nb; 300nb; 400nb; 500nb; 600nb; 700nb; 800nb; 900nb; or 1000nb. More preferably still said RNA molecule is at least 1000nb.

In a further preferred embodiment of the invention said RNA molecule comprises sequences identified in Table 4 or Figures 4-54.

In yet a further preferred embodiment of the invention said RNA molecules comprise modified nucleotide bases.

It will be apparent to one skilled in the art that the inclusion of modified bases, as well as the naturally occuring bases cytosine, uracil, adenosine and guanosine, may confer advantageous properties on RNA molecules containing said modified bases. For example, modified bases may increase the stability of the RNA molecule thereby reducing the amount required to produce a desired effect. The provision of modified bases may also provide stem-loop structures which are more or less stable.

According to a further aspect of the invention there is provided a nucleic acid molecule encoding at least part of a gene which mediates at least one step in stem cell differentiation comprising a first part linked to a second part which first and second parts are complementary over at least part of their length, wherein said nucleic acid molecule is operably linked to at least one further nucleic acid molecule capable of promoting transcription of said nucleic acid linked thereto and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length as or when said nucleic acid molecule is transcribed.

In a preferred embodiment of the invention said first and second parts are linked by linking nucleotides as hereinbefore described.

It will be apparent to one skilled in the art that the synthesis of RNA molecules which form RNA stem loops can be achieved by providing vectors which include target genes, or fragments of target genes, operably linked to promoter sequences. Typically, promoter sequences are phage RNA polymerase promoters (eg T7, T3, SP6). Advantageously vectors are provided with multiple cloning sites into which genes or gene fragments can be subcloned. Typically, vectors are engineered so that phage promoters flank multiple cloning sites containing the gene of interest.

Alternatively target genes or fragments of target genes can be fused directly to phage promoters by creating chimeric promoter/gene fusions via oligo synthesising technology. Constructs thus created can be easily amplified by polymerase chain reaction to provide templates for the manufacture of RNA molecules comprising stem loop RNA's.

According to a further aspect of the invention there is provided a vector including an expression cassette comprising a first sequence linked to a second sequence wherein said first and second sequences are complementary over at least part of their lengths and further wherein the expression cassette is transciptionally linked to a promoter sequence.

In a preferred embodiment of the invention said first and second parts are linked by linking nucleotides as hereinbefore described.

Vectors including expression cassettes encoding stem-loop RNA's are adapted for eukaryotic gene expression. Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell/tissue specific expression. These promoter sequences may be cell/tissue specific, inducible or constitutive.

Promoter elements typically also include so called TATA box and RNA polymerase initiation selection sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.

Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors. Further adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination sequences.

These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and references therein; Marston, F (1987) DNA Cloning Techniques: A Practical Approach Vol III IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons, Inc.(1994).

According to a further aspect of the invention there is provided a cell transfected with the nucleic acid or vector according to the invention. Preferably said cell is an embryonic stem cell or embryonic germ cell. Alternatively said cell is an embryonal carcinoma cell.

According to a further aspect of the invention there is provided a method to manufacture stem loop RNA molecules comprising:

(i) providing a vector or promoter/gene fusion according to the invention;

(ii) providing reagents and conditions which allow the synthesis of the RNA molecule comprising a stem loop RNA molecule according to the invention; and

(iii) providing conditions which allow the RNA molecule to base pair over at least part of its length, or at least that part corresponding to the nucleic acid sequence encoding said stem cell gene which mediates stem cell differentiation.

Preferably said gene, or gene fragment is selected from those genes represented in table 4 or Figures 4-54.

In vitro transcription of RNA is an established methodology. Kits are commercially available which provide vectors, ribonucleoside triphosphates, buffers, Rnase inhibitors, RNA polymersases (eg phage T7, T3, SP6) which facilitate the production of RNA.

According to a further aspect of the invention there is provided an *in vivo* method to promote the differentiation of stem cells comprising administering to an animal an effective amount of stem loop RNA molecule, or vector encoding a stem loop RNA molecule according to the invention, sufficient to effect differentiation of a target stem cell.

Preferably said method promotes differentiation *in vivo* of endogenous stem cells to repair tissue damage *in situ*.

It will be apparent to one skilled in the art that stem loop RNA relies on homology between the target gene RNA and double stranded region of the stem loop in a similar way to conventional RNAi. This confers a significant degree of specificity to the stem loop RNA molecule in targeting stem cells. For example, haemopoietic stem cells are found in bone marrow and stem loop RNA molecules may be administered to an animal by direct injection into bone marrow tissue.

Stem loop RNA molecules may be encapsulated in liposomes to provide protection from an animals immune system and/or nucleases present in an animals serum.

Liposomes are lipid based vesicles which encapsulate a selected therapeutic agent which is then introduced into a patient. Typically, the liposome is manufactured either from pure phospholipid or a mixture of phospholipid and phosphoglyceride. Typically liposomes can be manufactured with diameters of less than 200nm, this enables them to be intravenously injected and able to pass through the pulmonary capillary bed. Furthermore the biochemical nature of liposomes confers permeability across blood vessel membranes to gain access to selected tissues. Liposomes do have a relatively short half-life. So called STEALTH^R liposomes have been developed which comprise liposomes coated in polyethylene glycol (PEG). The PEG treated liposomes have a significantly increased half-life when administered intravenously to a patient. In addition STEALTH^R liposomes show reduced uptake in the reticuloendothelial system and enhanced accumulation selected tissues. In addition, so called immuno-liposomes have been develop which combine lipid based vesicles with an antibody or antibodies, to increase the specificity of the delivery of the RNAi molecule to a selected cell/tissue.

The use of liposomes as delivery means is described in US5580575 and US 5542935.

It will be apparent to one skilled in the art that the stem loop RNA molecules can be provided in the form of an oral or nasal spray, an aerosol, suspension, emulsion, and/or eye drop fluid. Alternatively the stem loop RNA molecules may be provided in tablet form. Alternative delivery means include inhalers or nebulisers.

According to a yet further aspect of the invention there is provided a therapeutic composition comprising a stem loop RNA molecule according to the invention or a vector encoding a stem loop RNA according to the invention.

Preferably said stem loop RNA molecule or vector is for use in the manufacture of a medicament for use in promoting the differentiation of stem cells to provide

differentiated cells/tissues to treat diseases where cell/tissues are destroyed by said disease.

Typically this includes pernicious anemia; stroke, neurodegenerative diseases such as Parkinson's disease, Alzhiemer's disease; coronary heart disease; cirrhosis; diabetes. It will also be apparent that differentiated stem cells may be used to replace nerves damaged as a consequence of (eg replacement of spinal cord tissue).

In a further preferred embodiment of the invention said therapeutic composition further comprises a diluent, carrier or excipient.

According to a further aspect of the invention there is provided a cell obtainable by the method according to the invention.

It will be apparent that a cell obtainable by the method according to the invention has useful applications . For example, a stably transfected cell under the control of a regulatable promoter (ie inducible, repressible, developmentally regulated, cell lineage regulated, cell-cycle regulated) offers the opportunity to modulate the expression of the stem-loop RNA in said cell thereby modulating the differentiation state, or not as the case maybe, in culture or *in vivo*.

According to a yet further aspect of the invention there is provided at least one organ comprising at least one cell obtainable by the method according to the invention.

According to a yet further aspect of the invention there is provided a non-human transgenic animal comprising a RNA molecule according to the invention, or a nucleic acid molecule according to the invention, or a vector according to the invention.

An embodiment of the invention will now be described by example only and with reference to the following figures and tables wherein:

Table 1 represents a selection of antibodies used to monitor stem cell differentiation;

Table 2 represents nucleic acid probes used to assess mRNA markers of stem differentiation;

Table 3 represents protein markers of stem cell differentiation;

Table 4 represents specific primers used to generate stem loop RNA for gene specific inhibition;

Table 5 represents vectors used for the expression of stem loop RNA in cells including the promoters used to drive transcription of stem loop RNA's.

Figure 1 illustrates stem cell differentiation is controlled by positive and negative regulators (A). The specific cell phenotypes that are derived are a direct result of positive and negative regulators which activate or suppress particular differentiation events. Stem loop RNA can be used to control both the initial differentiation of stem cells (A) and the ultimate fate of the differentiated cells D1 and D2 by repression of positive activators which would normally promote a particular cell fate;

Figure 2 represents the Oct 4 nucleic acid sequence from position 610-1032 of the sequence found in GenBank accession number NM_002701.

Fig 3A illustrates a transcription cassette comprising a promoter sequence operable linked to a nucleic acid encoding a stem loop RNA; Fig 3B illustrates a stem loop RNA synthesised from the cassette illustrated in Fig 1A;

Figure 4 is the nucleic acid sequence of murine notch ligand delta-like 1;

Figure 5 is the nucleic acid sequence of murine notch ligand jagged 1;

Figure 6 is the nucleic acid sequence of human notch ligand jagged 1 (alagille syndrome) (JAG1);

Figure 7 is the nucleic acid sequence of human notch ligand jagged 2 (JAG2)

Figure 8 is the nucleic acid sequence of murine notch ligand jagged 2;

Figure 9 is the nucleic acid sequence of human notch ligand delta-like 3 (DLL3);

Figure 10 is the nucleic acid sequence of human notch ligand delta-1 (DLL1);

Figure 11 is the nucleic acid sequence of human notch ligand delta-like 4 (DLL4);

Figure 12 is the nucleic acid sequence of murine notch ligand delta-like 4(DLL4);

Figure 13 represents the nucleic acid sequence of human *Wnt 13*;

Figure 14 represents the nucleic acid sequence of human *dickkopf1*;

Figure 15 represents the nucleic acid sequence of human *dickkopf2*;

Figure 16 represents the nucleic acid sequence of human *dickkopf3*; and

Figure 17 represents the nucleic acid sequence of human *dickkopf4*;

Figure 18 represents the nucleic acid sequence of WNT-1;

Figure 19 represents the nucleic acid sequence of WNT-2;

Figure 20 represents the nucleic acid sequence of WNT 2B;

Figure 21 represents the nucleic acid sequence of WNT 3;

Figure 22 represents the nucleic acid sequence of WNT 4;

Figure 23 represents the nucleic acid sequence of WNT 5A;

Figure 24 represents the nucleic acid sequence of WNT 6;

Figure 25 represents the nucleic acid sequence of WNT 7A;

Figure 26 represents the nucleic acid sequence of WNT 8B;

Figure 27 represents the nucleic acid sequence of WNT 10B;

Figure 28 represents the nucleic acid sequence of WNT 11;

Figure 29 represents the nucleic acid sequence of WNT 14

Figure 30 represents the nucleic acid sequence of WNT 16;

Figure 31 represents the nucleic acid sequence of FZD 1;

Figure 32 represents the nucleic acid sequence of FZD 2;

Figure 33 represents the nucleic acid sequence of FZE 3;

Figure 34 represents the nucleic acid sequence of FZD 4;

Figure 35 represents the nucleic acid sequence of FZD 5;

Figure 36 represents the nucleic acid sequence of FZD 6;

Figure 37 represents the nucleic acid sequence of FZD 7;

Figure 38 represents the nucleic acid sequence of FZD 8;

Figure 39 represents the nucleic acid sequence of FZD 9;

Figure 40 represents the nucleic acid sequence of FZD 10;

Figure 41 represents the nucleic acid sequence of FRP;

Figure 42 represents the nucleic acid sequence of SARP 1;

Figure 43 represents the nucleic acid sequence of SARP 2;

Figure 44 represents the nucleic acid sequence of FRZB;

Figure 45 represents the nucleic acid sequence of FRPHE;

Figure 46 represents the nucleic acid sequence of SARP 3;

Figure 47 represents the nucleic acid sequence of CER 1;

Figure 48 represents the nucleic acid sequence of DKK1;

Figure 49 represents the nucleic acid sequence of DKK 2;

Figure 50 represents the nucleic acid sequence of DKK 3;

Figure 51 represents the nucleic acid sequence of DKK 4;

Figure 52represents the nucleic acid sequence of WIF-1;

Figure 53 represents the nucleic acid sequence of SRFP 1;

Figure 54 represents the nucleic acid sequence of SRFP 4;

Materials and Methods

Cell Culture

NTERA2 and 2102Ep human EC cell lines were maintained at high cell density as previously described (Andrews et al 1982, 1984b), in DMEM (high glucose formulation) (DMEM)(GIBCO BRL), supplemented with 10% v/v bovine foetal calf serum (GIBCO BRL), under a humidified atmosphere with 10% CO_2 in air.

Stem Loop RNA Production

Primers were designed against specific target genes with T7 bacteriophage promoters at their 5' ends . The primers consist of typically 18- 25 bp against the target gene, a linker sequence of variable length (indicated by N in primer sequence) followed by the reverse complement of the gene specific sequence. The primers were used in a standard RNA in vitro. transcription reaction using a MEGASCRIPT kit following manufacturers protocols (Ambion, USA). Longer slRNA templates were produced buy cloning head-to –tail the sense and anti-sense gene specific sequences to generate a palindromic template from which RNA could be synthesized.

The following primers were used

Gene	Accession Number	Primer Sequence
Oct4	Z11899	TAA TAC GAC TCA CTA TAG Ggagcagcttgggctcgagaag(N)cttctcgagcccaagctgctc
HsNotch2		TAA TAC GAC TCA CTA TAGGt cgt gca aga gcc agt tac cc(N)gg gta act ggc tct tgcacg a
HsNotch1	M73980	TAA TAC GAC TCA CTA TAGGa atg gtc aat gcg agt ggc tgt cc(N)gg aca gcc act cgc gtt gac cat t
CIF		TAA TAC GAC TCA CTA TAGGa gta gtg aga gtg aga gta aca(N)tgt tac tct cac tct cac tac t
RBPJ-kappa		TAA TAC GAC TCA CTA TAGGt cctgtg cctgtg gta gag a(N)t ctc tac cac agg cac agg a
Dlk1	NM_002226	TAA TAC GAC TCA CTA TAGGcctc ttg ctc ctg ctg gct tt(N)aaagccagcaggagcaagagg

Capital letters indicate the T7 polymerase promoter sequence.

In each case, a quantity of the PCR was electrophoresed through agarose to verify product size and abundance, whilst the remainder was purified by alkaline phenol/chloroform extraction. RNA was synthesized using the Megascript kit (Ambion Inc.) according to the manufacturer's protocol and acid phenol/chloroform extracted. The simultaneous synthesis of complementary strands of RNA in a single reaction circumvents the requirement for an annealing step. However, the quality and duplexing of the synthesized RNA was confirmed by agarose gel electrophoresis, with the desired products migrating as expected for double stranded DNA of the same length.

Stem Loop RNA introduction to Cell Lines

Human EC stem cells were seeded at 2 X10^5 cells/well of a 6 well plate in 3 cm^3 of Dulbecco's modified Eagles medium and allowed to settle for 3 hrs.
Appx. 9.5μg of DNA was incubated with an optimised amount of ExGEN 500 for each well of a 6-well plate. Previously cells were seeded 1 day before. This gives apprx. a 70% confluent culture. The DNA/ExGen mixture was added to the cells and the culture vessel spun at 280g for 5 mins.

Total RNA production

Growing cultures of cells were aspirated to remove the DME and foetal calf serum. Trace amounts of foetal calf serum was removed by washing in Phosphate-buffered saline. Fresh PBS was added to the cells and the cells were dislodged from the culture vessel using acid washed glass beads. The resulting cell suspension was centrifuged at 300xg. The pellets had the PBS aspirated from them. Tri reagent (Sigma, USA) was added at 1ml per 10^7 cells and allowed to stand for 10 mins at room temperature. The lysate from this reaction was centrifuged at 12000 x g for 15 minutes at 4°C. The resulting aqueous phase was transferred to a fresh vessel and 0.5 ml of isopropanol / ml of trizol was added to precipitate the RNA. The RNA was pelleted by centrifugation at 12000 x g for 10 mins at 4°C. The supernatant was removed and the pellet washed in 70% ethanol. The washed RNA was dissolved in DEPC treated double-distilled water.

Analysis of the differentiation of EC stem cells induced by exposure to Stem Loop RNA

Following exposure to stem loop RNA corresponding to specific key regulatory genes, the subsequent differentiation of the EC cells was monitored in a variety of ways. One approach was to monitor the disapearance of typical markers of the stem cell phenotype; the other was to monitor the appearance of markers pertinent to the specific lineages induced. The relevant markers included surface antigens, mRNA species and specific proteins.

Analysis of Transfectants by Antibody Staining and FACS

Cells were treated with trypsin (0.25% v/v) for 5 mins to disaggregate the cells; they were washed and re-suspended to $2x10^5$ cells/ml. This cell suspension was incubated with 50µl of primary antibody in a 96 well plate on a rotary shaker for 1 hour at 4°C. Supernatant from a myeloma cell line P3X63Ag8, was used as a negative control. The 96 well plate was centrifuged at 100rpm for 3 minutes. The plate was washed 3 times with PBS containing 5% foetal calf serum to remove unbound antibody. Cell

were then incubated with 50 µl of an appropriate FITC-conjugated secondary antibody at 4°C for 1 hour. Cells were washed 3 times in PBS + 5% foetal calf serum and analysed using an EPICS elite ESP flow cytometer (Coulter eletronics, U.K).(Andrews et. al., 1982)

Northern blot Analysis of RNA

RNA separation relies on the generally the same principles as standard DNA but with some concessions to the tendancy of RNA to hybridise with itself or other RNA molecules. Formaldehyde is used in the gel matrix to react with the amine groups of the RNA and form Schiff bases. Purified RNA is run out using standard agarose gel electrophresis. For most RNA a 1% agarose gel is sufficiant. The agarose is made in 1X MOPS buffer and supplemeted with 0.66M formaldehyde.Dryed down RNA samples are reconstituted and denatured in RNA loading buffer and loaded into the gel. Gels are run out for apprx. 3 hrs (until the dye front is 3/4 of the way down the gel).

The major problem with obtaining clean blotting using RNA is the presence of formaldehyde. The run out gel was soaked in distilled water for 20 mins with 4 changes, to remove the formaldehyde from the matrix. The transfer assembly was assembled in exactly the same fashion as for DNA (Southern) blotting.The transfer buffer used however was 10X SSPE. Gels were transfered overnight. The membrane was soaked in 2X SSPE to remove any agarose from the transfer assembly and the RNA was fixed to the memebrane. Fixation was acheived using short-wave (254 nM) UV light. The fixed membrane was baked for 1-2 hrs to drive off any residual formaldehyde.

Hybridisation was acheived in aqueous phase with formamide to lower the hybridisation temperatures for a given probe. RNA blots were prehybridised for 2-4 hrs in northern prehybridisation soloution. Labelled DNA probes were denatured at 95°C for 5 mins and added to the blots. All hybridisation steps were carried out in rolling bottles in incubation ovens. Probes were hybridised overnight for at least 16

hrs in the prehybridisation soloution. A standard set of wash soloutions were used. Stringency of washing was acheived by the use of lower salt containing wash buffers. The following wash procedure is outlined as follows

2X SSPE	15 mins	room temp
2X SSPE	15 mins	room temp
2X SSPE/ 0.1% SDS	45 mins	65°C
2X SSPE/ 0.1% SDS	45 mins	65°C
0.1X SSPE	15 mins	room temp

Preparation of radiolabelled DNA probes

The method of Feinberg and Vogelstein (Feinberg and Vogelstein, 1983) was used to radioactively label DNA. Briefly, the protocol uses random sequence hexanucleotides to prime DNA synthesis at numerous sites on a denatured DNA template using the Klenow DNA polymerase I fragment. Pre-formed kits were used to aid consistency . 5-100ng DNA fragment (obtained from gel purifcation of PCR or restriction digests) was made up in water,denatured for 5 mins at 95°C with the random hexamers. The mixture was quench cooled on ice and the following were added,

5 µl [α-32P] dATP 3000 Ci/mmol

1 µl of Klenow DNA polymerase (4U)

The reaction was then incubated at 37°C for 1 hr. Unincorporated nucleotide were removed with spin columns (Nucleon Biosciences).

Production of cDNA

The enzymatic conversion of RNA into single stranded cDNA was achieved using the 3' to 5' polymerase activity of recombinant Moloney-Murine Leukemia Virus (M-MLV) reverse transcriptase primed with oligo (dT) and (dN) primers. For Reverse Transcription-Polymerase Chain Reaction, single stranded cDNA was used. cDNA was synthesised from 1µg poly (A)+ RNA or total RNA was incubated with the following

1.0µM oligo(dT) primer for total RNA or random hexcamers for mRNA

0.5mM 10mM dNTP mix

1U/μl RNAse inhibitor (Promega)

1.0U/μl M-MLV reverse transcriptase in manufacturers supplied buffer (Promega)

The reaction was incubated for 2-3 hours at 42°C

Fluorescent Automated Sequencing

To check the specificity of the PCR primers used to generate the template used in stem loop RNA production automatic sequencing was carried out using the prism fluorescently labelled chain terminator sequencing kit (Perkin-Elmer) (Prober et al 1987). A suitable amount of template (200ng plasmid, 100ng PCR product), 10 μM sequencing primer (typically a 20mer with 50% G-C content) were added to 8 μl of prism pre-mix and the total reaction volume made up to 20 μl. 24 cycles of PCR (94°C for 10 seconds, 50°C for 10 seconds, 60°C for 4 minutes). Following thermal cycling, products were precipitated by the addition of 2μl of 3M sodium acetate and 50 μl of 100 % ethanol. DNA was pelleted in an Eppendorf microcentrifuge at 13000 rpm, washed once in 70% ethanol and vacuum dried. Samples were analysed by the in-house sequencing Service (Krebs Institute). Dried down samples were resuspended in 4 μl of formamide loading buffer, denatured and loaded onto a ABI 373 automatic sequencer. Raw sequence was collected and analysed using the ABI prism software and the results were supplied in the form of analysed histogram traces.

Detection of specific protein targets by SDS-PAGE and Western Blotting

To obtain cell lysates monolayers of cells were rinsed 3 times with ice-cold PBS supplemented with 2 mM $CaCl_2$. Cells were incubated with 1 ml/75 cm^2 flask lysis buffer (1% v/v NP40, 1% v/v DOC, 0.1 mM PMSF in PBS) for 15 min at 4°C. Cell lysates were transferred to eppendorf tubes and passed through a 21 gauge needle to shear the DNA. This was followed by freeze thawing and subsequent centrifugation (30 min, 4°C, 15000*g*) to remove insoluble material. Protein concentrations of the

supernatants were determined using a commercial protein assay (Biorad). Samples were prepared for SDS-PAGE by adding 6 times Laemmli electrophoresis sample buffer and boiling for 5 min. After electrophoresis with 16 μg of protein on a 10% polyacrylamide gel (Laemmli, 1970) the proteins were transferred to PVDF membrane. The blots were washed with PBS and 0.05% Tween (PBS-T). Blocking of the blots occurred in 5% milk powder in PBS-T (60 min, at RT). Blots were incubated with the appropriate primary antibody. Horseradish peroxidase labelled secondary antibody was used to visualise antibody binding by ECL (Amersham, Bucks., UK). Materials used for SDS-PAGE and western blotting were obtained from Biorad (California, USA) unless stated otherwise.

Table 1: Antibodies used to detect stem cell differentiation

Antibody	**Class**	**Species**	**Cell phenotype detected**	**Changes on Differentiation**	**Reference**
TRA-1-60	IgM	Mouse	Human EC, ES cells.	↓ differentiation	Andrews et.al., 1984a
TRA-1-81	IgM	Mouse	Human EC, ES cells.	↓ differentiation	Andrews et. al.,1984a
SSEA3	IgM	Rat	Human EC, ES cells.	↓ differentiation	Shevinsky et al 1982, Fenderson et al 1987
SSEA4	IgG	Mouse	Human EC, ES cells.	↓ differentiation	Kannagi et al 1983 Fenderson et al 1987
A2B5	IgM	Mouse		↑ differentiation	Fenderson et al 1987
ME311	IgG	Mouse		↑ differentiation	Fenderson et al 1987
VIN-IS-56	IgM	Mouse		↑ differentiation	Andrews et al 1990
VIN-IS-53	IgG	Mouse		↑ differentiation	Andrews et al 1990

Table 2: Probes used to assess mRNA markers of differentiation

Gene	Cell Type
Synaptophysin	Neuron
NeuroD1	Neuron
MyoD1	Muscle
Collagens	Cartlidge
Alpha-actin	Skeletal muscle
Smooth-muscle actin	Smooth muscle

Table 3: Protein markers of differentiation, detected by Western Blot and/or immunofluorescence.

The following antibodies were detected by the appropriate commercially available antibodies

Cell Type	Antigen
Neurons	Neurofilaments
Glial cells	GFAP
Epithelial cells	Cytokeratins
Mesenchymal cells	Vimentin
Muscle	Desmin
Muscle	Tissue specific actins
Connective tissue cells	Collagens

Table 4: Specific Primers used to generate Stem Loop RNA for gene specific inhibition

All sequences written 5' to 3'

	Gene Name	**Accession number**	**PCR primer Sequences**	**Position**
Notch Pathway				
Ligands:				
	Dll-1	AF003522		
	Dll3	NM_016941		
	Dll4	NM_019454		
	Dlk-1	NM_003836		
	Jagged1	U73936		
	Jagged2	NM_002226		
Receptors:				
	Notch1	M73980	gcggccgcctttgtggttctgttc gccggcgcgtcctcctcttcc	5224-5726
	Notch2	In-house sequence	gccagaatgatgctacctgt tagagcagcaccaatggaac	
	Notch3	U97669	Aagttacccccaagaggcaagtgtt Aaggaaatgagaggccagaaggaga	7013-7348
	Notch4	U95299	ggctgcccctcccactctcg cagcccgggccccaggatag	3727-4132
Downstream:				
	TLE-1	NM_005077		
	TLE-2	M99436		
	TLE-3	M99438		
	TLE-4	M99439		

	TCF7	NM_003202		
	TCFFL2	Y11306		
	TCF3	M31523		
	TCF19	NM_007109		
	TCF1	NM_000545		
	mfringe	NM_002405		
	lfringe	U94354		
	rFringe	AF108139		
	Se11	AF157516		
	Numb	NM_003744		
	LNX	NM_010727		
Wingless Pathway				
Ligands				
	Wnt1	NM_005430		
	Wnt2	NM_003391		
	Wnt2B	NM_004185	tgagtggttcctgtactctg actcacactgggtaacacgg	1159-1503
	Wnt5A	L20861		
	Wnt6	AF079522		
	Wnt7A	NM_004625		
	Wnt8B	NM_003393		
	Wnt10B	NM_003394		
	Wnt11	NM_004626		
	Wnt14	AF028702		
	Wnt15	AF028703		
	Wnt16	AF169963		
Receptors				
	FZD1	NM_003505		
	FZD2	NM_001466	tacccagagcggcctatcattttt	955-1439

			acgaagccggccaggaggaagga c	
	FZD3	NM_017412		
	FZD4	NM_012193		
	FZD5	NM_003468		
	FZD6	NM_003506	Tggcctgaggagcttgaatgtgac Atcgcccagcaaaaatccaatgaa	607-1026
	FZD7	NM_003507		
	FZD8	AA481448		
	FZD9	NM_003508		
	FZD10	NM_007197		
	FRZB	NM_001463		
Extracellular Effectors				
	SFRP1	NM_003012		
	SFRP2	AF017986		
	SFRP4	AF026692	agaggagtggctgcaatgaggtc gcgcccggctgttttctt	877-1178
	SFRP5	NM_003015		
	SK	AB020315		
	CER1	NM_005454		
	WIF-1	NM_007191		
	DVL1	U46461		
	DVL2	NM_004422		
	DVL3	NM_004423		
Transcription Factors				
	Oct4	Z11899		
	Brachyury	NM_003181		

	NeuroD1	NM_002500		
	NeuroD2	NM_006160		
	NeuroD3	U63842		
	MyoD	NM_002478		
	MDFI	NM_005586		
	REST	NM_005612		

Table 5

Listed are examples of vector systems that are to be used in cells to direct the production of stem loop RNA.

Expression System	Vectors	Accession numbers	Promoters
Tet-on/Tet-off Clontech, USA	pTet-on pTet-off pTRE2-Hyg	U89930 U89929	CMV MyoD1 NeuroD1 Oct4 GATA1 Beta-actin PGK
IRES Invitrogen, Nethelands)	pIRES-EGFP		CMV MyoD1 NeuroD1 Oct4 GATA1 Beta-actin PGK
Ecdysone Invitrogen, Netherlands	pIND pVgRXR		CMV MyoD1 NeuroD1 Oct4 GATA1 Beta-actin PGK

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CLAIMS

1. A method to modulate the differentiation state of a stem cell comprising:

i) contacting a stem cell with at least one nucleic acid molecule comprising a sequence of a gene which mediates at least one step in the differentiation of said cell which nucleic acid molecule consists of a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length;

(ii) providing conditions conducive to the growth and differentiation of the cell treated in (i) above; and optionally

(iii) maintaining and/or storing the cell in a differentiated state.

2. A method according to Claim 1 wherein said first and second parts are linked by at least one nucleotide base.

3 A method according to Claim 1 or 2 wherein said nucleic acid molecule is a stem loop RNA molecule or a nucleic acid molecule or a vector encoding said stem loop RNA.

4. A method according to any of Claims 1-3 wherein said conditions are *in vitro* cell culture conditions.

5. A method according to any of Claims 1-4 wherein said stem cell is selected from the group consisting of: an embryonic stem cell; an embryonic germ cell; an embryonal carcinoma cell; a haemopoietic stem cell; a muscle stem cell; a nerve stem cell; a skin dermal sheath stem cell; a liver stem cell; a teratocarcinoma cell.

6. A method according to any of Claims 1-5 wherein said stem cell is an embryonic stem cell or embryonic germ cell.

7. A method according to any of Claims 1-6 wherein said nucleic acid molecule is derived from at least one nucleic acid sequence as represented by Figures 4- 54.

8. A RNA molecule derived from a coding sequence of at least one gene involved in stem cell differentiation comprising a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length.

9. A RNA molecule according to Claim 8 wherein said first and second parts are linked by at least one nucleotide base (nb).

10. A RNA molecule according to Claim 9 wherein said first and second parts are linked by 2, 3, 4, 5, 6, 7, 8, 9, or 10nb in length.

11. A RNA molecule according to Claim 9 wherein said linker is at least 10nb in length.

12. A RNA molecule according to any of Claims 8-11 wherein the length of the RNA molecule is between 10nb –1000nb in length.

13. A RNA molecule according to Claim 12 wherein the length of the RNA molecule is selected from 10nb; 20nb; 30nb; 40nb; 50nb; 60nb; 70nb; 80nb; 90nb in length.

14. A RNA molecule according to Claim 12 wherein said RNA molecule is 100nb; 200nb; 300nb; 400nb; 500nb; 600nb; 700nb; 800nb; 900nb; or 1000nb in length.

15. A RNA molecule according to Claim 8 wherein said RNA molecule is at least 1000nb in length.

16. A RNA molecule according to Claim 8 wherein said RNA molecule is 21nb in length.

17. A RNA molecule according to any of Claims 8 -16 wherein said RNA molecule comprises sequences identified in Figures 4-54.

18. A RNA molecule according to any of Claims 8-17 wherein said RNA molecules comprise modified nucleotide bases.

19. A nucleic acid molecule which encodes an RNA molecule according to any of Claims 8-18 wherein said nucleic acid molecule is operably linked to at least one further nucleic acid molecule capable of promoting transcription of said nucleic acid linked thereto.

20. A nucleic acid molecule according to Claim 19 wherein said further nucleic acid molecule is a promoter capable of inducible transcription.

21. A vector including a nucleic acid molecule according to Claim 19 or 20.

22. A cell transfected with an RNA molecule according to any of Claims 8-18, nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21.

23. A cell according to Claim 22 wherein said cell is an embryonic stem cell or embryonic germ cell.

24. A cell according to Claim 22 wherein said cell is an embryonal carcinoma cell.

25. A method to manufacture stem loop RNA molecules comprising:

(i) providing a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21;

(ii) providing reagents and conditions which allow the synthesis of the RNA molecule comprising a RNA molecule according to any of Claims 8-18; and

(iii) providing conditions which allow the RNA molecule to base pair over at least part of its length, or at least that part corresponding to the nucleic acid sequence encoding said stem cell gene which mediates stem cell differentiation.

26. An *in vivo* method to promote the differentiation of stem cells comprising administering to an animal an effective amount of an RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21, sufficient to effect differentiation of a target stem cell.

27. A RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21 for use as a pharmaceutical.

28. A pharmaceutical composition comprising a RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21.

29. Use of a RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21 for the manufacture of a medicament for use in promoting the differentiation of stem cells to provide differentiated cells/tissues to treat diseases where cell/tissues are destroyed by said disease.

30 Use according to Claim 29 wherein said disease is selected from the group consisting of: pernicious anemia; stroke, neurodegenerative diseases such as Parkinson's disease, Alzhiemer's disease; coronary heart disease; cirrhosis; diabetes; nerves damaged as a consequence of trauma (e.g. replacement of spinal cord tissue).

31. A cell obtainable by the method according to any of Claims 1-7.

32. An organ comprising at least one cell according to Claim 31.

33. A non-human transgenic animal comprising a RNA molecule according to any of Claims 8-18, or a nucleic acid molecule according to Claim 19 or 20, or a vector according to Claim 21.

Figure 1

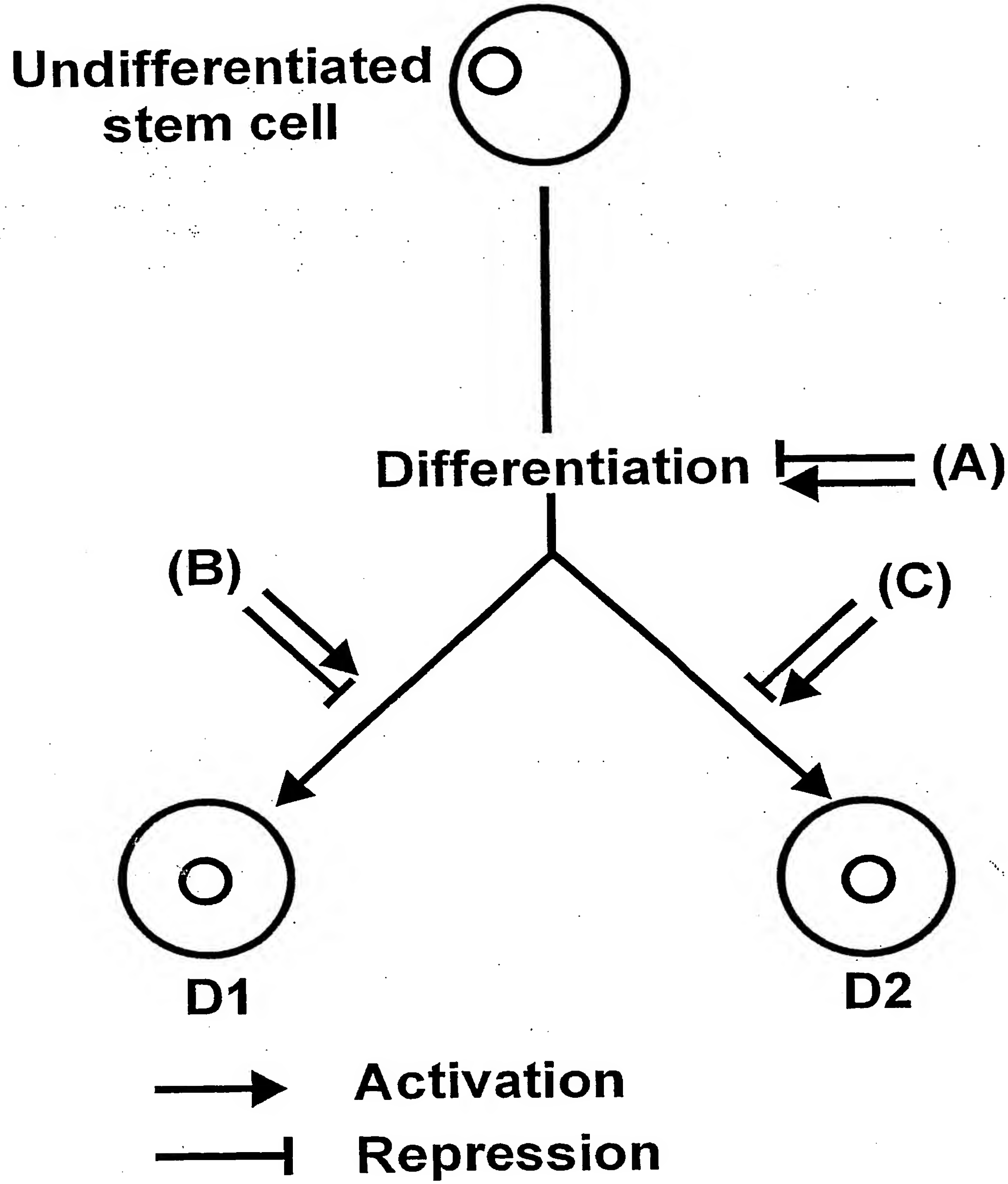
Undifferentiated stem cell
Differentiation
(A)
(B)
(C)
D1
D2
Activation
Repression

Figure 2

5'
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CTGAGGTGCCTGCCTGCCCTTCTAGGAATGGGGGACAGGGGGAGGGGAGGAGCTAG
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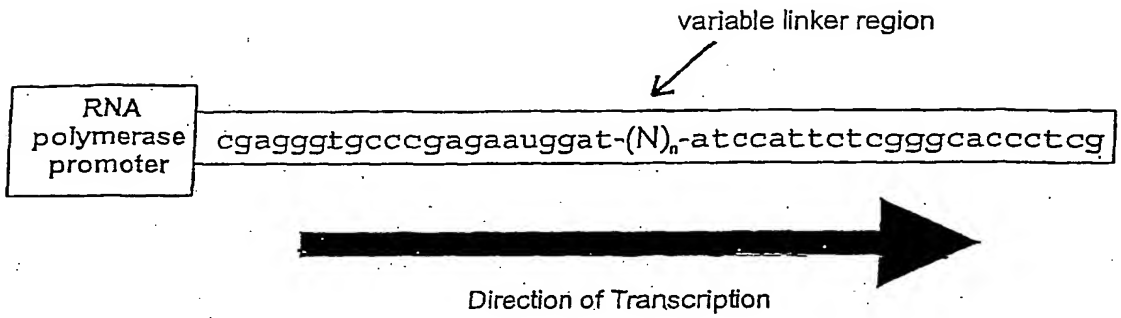
GGAAGGAATTGGGAACACAAAGGG
3'

A



B

5'-cgagggtgcccgagaatggat-$(N)_n$

3'-$(N)_n$-gctcccacgggctcttacctaa-$(N)_n$

Figure 3

Figure 3

GTCCAGCGGTACCATGGGCCGTCGGAGCGCGCTAGCCCTTGCCGTGGTCTCTGCCCTGCTGTGC
CAGGTCTGGAGCTCCGGCGTATTTGAGCTGAAGCTGCAGGAGTTCGTCAACAAGAAGGGGCTG
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AAGCCCTCCATACAGACTCTCCCGATGACCTCGCAACAGAAAACCCAGAAAGACTCATCAGCC
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Figure 4

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Figure 5

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Figure 6

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CCCTGCCGGAACGGCGCTCGCTGCTATAACCTGGAGGGTGACTATTACTGCGCCTGCCCTGATGACTTTG
GTGGCAAGAACTGCTCCGTGCCCCGCGAGCCGTGCCCTGGCGGGGCCTGCAGAGTGATCGATGGCTGCGG

GTCAGACGCGGGGCCTGGGATGCCTGGCACAGCAGCCTCCGGCGTGTGTGGCCCCCATGGACGCTGCGTC
AGCCAGCCAGGGGGCAACTTTTCCTGCATCTGTGACAGTGGCTTTACTGGCACCTACTGCCATGAGAACA
TTGACGACTGCCTGGGCCAGCCCTGCCGCAATGGGGGCACATGCATCGATGAGGTGGACGCCTTCCGCTG
CTTCTGCCCCAGCGGCTGGGAGGGCGAGCTCTGCGACACCAATCCCAACGACTGCCTTCCCGATCCCTGC
CACAGCCGCGGCCGCTGCTACGACCTGGTCAATGACTTCTACTGTGCGTGCGACGACGGCTGGAAGGGCA
AGACCTGCCACTCACGCGAGTTCCAGTGCGATGCCTACACCTGCAGCAACGGTGGCACCTGCTACGACAG
CGGCGACACCTTCCGCTGCGCCTGCCCCCCCGGCTGGAAGGGCAGCACCTGCGCCGTCGCCAAGAACAGC
AGCTGCCTGCCCAACCCCTGTGTGAATGGTGGCACCTGCGTGGGCAGCGGGGCCTCCTTCTCCTGCATCT
GCCGGGACGGCTGGGAGGGTCGTACTTGCACTCACAATACCAACGACTGCAACCCTCTGCCTTGCTACAA
TGGTGGCATCTGTGTTGACGGCGTCAACTGGTTCCGCTGCGAGTGTGCACCTGGCTTCGCGGGGCCTGAC
TGCCGCATCAACATCGACGAGTGCCAGTCCTCGCCCTGTGCCTACGGGGCCACGTGTGTGGATGAGATCA
ACGGGTATCGCTGTAGCTGCCCACCCGGCCGAGCCGGCCCCCGGTGCCAGGAAGTGATCGGGTTCGGGAG
ATCCTGCTGGTCCCGGGGCACTCCGTTCCCACACGGAAGCTCCTGGGTGGAAGACTGCAACAGCTGCCGC
TGCCTGGATGGCCGCCGTGACTGCAGCAAGGTGTGGTGCGGATGGAAGCCTTGTCTGCTGGCCGGCCAGC
CCGAGGCCCTGAGCGCCCAGTGCCCACTGGGGCAAAGGTGCCTGGAGAAGGCCCCAGGCCAGTGTCTGG
ACCACCCTGTGAGGCCTGGGGGAGTGCGGCGCAGAAGAGCCACCGAGCACCCCCTGCCTGCCACGCTC
GGCCACCTGGACAATAACTGTGCCCGCCTCACCTTGCATTTCAACCGTGACCACGTGCCCCAGGGCACCA
CGGTGGGCGCCATTTGCTCCGGGATCCGCTCCCTGCCAGCCACAAGGGCTGTGGCACGGGACCGCCTGCT
GGTGTTGCTTTGCGACCGGGCGTCCTCGGGGGCCAGTGCCGTGGAGGTGGCCGTGTCCTTCAGCCCTGCC
AGGGACCTGCCTGACAGCAGCCTGATCCAGGGCGCGGCCCACGCCATCGTGGCCGCCATCACCCAGCGG
GGAACAGCTCACTGCTCCTGGCTGTCACCGAGGTCAAGGTGGAGACGGTTGTTACGGGCGGCTCTTCCAC
AGGTCTGCTGGTGCCTGTGCTGTGTGGTGCCTTCAGCGTGCTGTGGCTGGCGTGCGTGGTCCTGTGCGTG
TGGTGGACACGCAAGCGCAGGAAAGAGCGGGAGAGGAGCCGGCTGCCGCGGGAGGAGAGCGCCAACAC
AGTGGGCCCCGCTCAACCCCATCCGCAACCCCATCGAGCGGCCGGGGGCCACAAGGACGTGCTCTACCA
GTGCAAGAACTTCACGCCGCCGCCGCGCAGGGCGGACGAGGCGCTGCCCGGGCCGGCCGGCCACGCGGC
GTCAGGGAGGATGAGGAGGACGAGGATCTGGGCCGCGGTGAGGAGGACTCCCTGGAGGCGGAGAAGTTC
TCTCACACAAATTCACCAAAGATCCTGGCCGCTCGCCGGGGAGGCCGGCCCACTGGGCCTCAGGCCCCAA
AGTGGACAACCGCGCGGTCAGGAGCATCAATGAGGCCCGCTACGCCGGCAAGGAGTAGGGGCGGCTGCG
CTGGGCCGGGACCCAGGGCCCTCGGTGGGAGCCATGCCGTCTGCCGGACCCGGAGCCGAGGCATGTGCT
AGTTTCTTTATTTTGTGTAAAAAAACCACCAAAAACAAAAACCAAATGTTTATTTTCTACGTTTCTTTAA
CCTTGTATAAATTATTCAGTAACTGTCAGGCTGAAAACAATGGAGTATTCTCGGATAGTTGCTATTTTTG
TAAAGTTTCCGTGCGTGGCACTCGCTGTATGAAAGGAGAGAGCAAAGGGTGTCTGCGTCGTCACCAAATC
GTAGCGTTTGTTACCAGAGGTTGTGCACTGTTTACAGAATCTTCCTTTTATTCCTCACTCGGGTTTCTCT
GTGGCTCCAGGCCAAAGTGCCGGTGAGACCCATGGCTGTGTTGGTGTGGCCCATGGCTGTTGGTGGGACC
CGTGGCTGATGGTGTGGCCTGTGGCTGTCGGTGGGACTCGTGGCTGTCAATGGGACCTGTGGCTGTCGGT
GGGACCTACGGTGGTCGGTGGGACCCTGGTTATTGATGTGGCCCTGGCTGCCGGCACGGCCCGTGGCTGT
TGACGCACCTGTGGTTGTTAGTGGGGCCTGAGGTCATCGGCGTGCCCAAGGCCGGCAGGTCAACCTCGCG
CTTGCTGGCCAGTCCACCCTGCCTGCCGTCTGTGCTTCCTCCTGCCCAGAACGCCCGCTCCAGCGATCTC
TCCACTGTGCTTTCAGAAGTGCCCTTCCTGCTGCGCAGTTCTCCCATCCTGGGACGGCGGCAGTATTGAA
GCTCGTGACAAGTGCCTTCACACAGACCCCTCGCAACTGTCCACGCGTGCCGTGGCACCAGGCGCTGCCC
ACCTGCCGGCCCCGGCCGCCCCTCCTCGTGAAAGTGCATTTTTGTAAATGTGTACATATTAAAGGAAGCA
CTCTGTATATTTGATTGAATAATGCCACCAAAAAAAAAAAAAAAAAAAAAATTCCTGCCC

Figure 7

TCGAGGCGGCGATGCGGGCACGCGGCTGGGGACGCCTGCCTCGGCGGCTGCTGCTGCTACTGG
TTCTGTGCGTGCAGGCGACGCGGCCCATGGGCTATTTCGAGCTGCAGCTGAGCGCGCTGCGGAA
CGTGAACGGGGAGCTGCTGAGCGGCGCCTGCTGTGACGGCGACGGCCGGACGACGCGCGCGGG
GGGCTGCGGCCGCGACGAGTGCGACACGTACGTGCGCGTGTGCCTTAAGGAGTACCAGGCCAA
GGTGACGCCCACGGGGCCCTGCAGCTACGGCTACGGCGCCACGCCCGTGCTGGGTGGCAACTC
CTTCTACCTGCCGCCGGCGGGCGCTGCGGGGGACCGAGCGCGCGCGCGGTCTCGGACCGGCGG
CCACCAGGACCCGGGCCTCGTCGTCATTCCCTTTCAGTTCGCCTGGCCGCGTTCTTTCACCCTCA
TCGTGGAGGCCTGGGACTGGGACAATGACACCACTCCAGATGAGGAGCTGCTGATTGAGCGGG
TGTCGCACGCTGGCATGATCAACCCCGAGGACCGCTGGAAGAGCCTGCACTTCAGCGGCCACG
TGGCACACCTGGAGCTGCAGATCCGAGTGCGCTGTGATGAGAACTACTACAGTGCCACCTGCA
ACAAGTTCTGCCGGCCCCGCAACGACTTCTTTGGCCACTATACCTGCGACCAGTACGGCAACAA
GGCCTGCATGGATGGCTGGATGGGCAAAGAATGCAAAGAAGCCGTGTGTAAACAAGGATGTAA
TTTGCTCCACGGGGGATGCACTGTGCCTGGGGAGTGCAGGTGCAGCTACGGCTGGCAGGGCAA

GTTCTGTGACGAGTGTGTCCCCTACCCTGGCTGCGTGCATGGCAGCTGTGTGGAGCCCTGGCAC
TGTGACTGTGAGACCAACTGGGGTGGCCTGCTCTGCGACAAAGACCTGAACTACTGTGGCAGC
CACCACCCCTGTGTCAACGGGGGTACCTGCATCAATGCTGAGCCTGACCAATACCTCTGCGCCT
GCCCAGATGGCTACTTGGGCAAGAACTGTGAGCGGGCTGAGCACGCCTGTGCCTCCAACCCGT
GTGCCAATGGGGGCTCTTGCCACGAAGTGCCATCTGGCTTTGAATGCCACTGTCCGTCAGGATG
GAGCGGACCCACCTGTGCGCTCGACATTGATGAGTGTGCCTCTAACCCATGTGCAGCGGGTGGT
ACCTGCGTGGATCAGGTGGACGGCTTCGAGTGCATCTGCCCGGAGCAGTGGGTGGGGGCTACT
TGCCAGCTGGACGCCAATGAGTGTGAAGGGAAGCCGTGCCTTAATGCTTTTTCTTGCAAAAACC
TGATTGGCGGCTATTACTGTGATTGCCTCCCGGGCTGGAAGGGCATCAACTGCCAAATCAACAT
CAACGATTGTCATGGGCAGTGTCAGCATGGGGGCACCTGCAAGGACCTGGTCAATGGGTACCA
GTGTGTGTGCCCGCGGGGCTTTGGAGGTCGCCATTGCGAACTAGAGTACGACAAGTGTGCCAG
CAGCCCCTGCCGCCGGGGTGGCATCTGCGAGGACCTGGTGGATGGCTTCCGCTGCCACTGCCCA
CGGGGCCTCTCTGGGCTGCACTGTGAGGTGGACATGGATCTCTGTGAACCAAGCCCCTGCCTCA
ACGGTGCTCGCTGCTACAACCTTGAGGGTGACTACTACTGCGCCTGCCCAGAAGACTTTGGTGG
CAAGAACTGCTCAGTGCCCAGGGACACATGCCCTGGCGGGGCATGTAGAGTGATCGATGGCTG
CGGGTTCGAGGCAGGGTCCAGGGCACGCGGTGTCGCACCCTCTGGTATATGTGGCCCTCACGG
GCACTGCGTTAGCCTGCCTGGGGGAAACTTCTCCTGCATCTGTGACAGCGGCTTCACAGGCACC
TACTGCCATGAAAACATTGACGACTGCATGGGCCAGCCCTGCCGCAACGGGGGCACGTGCATT
GACGAAGTGGACTCCTTCCGCTGCTTCTGCCCCAGTGGCTGGGAAGGAGAACTCTGTGACATCA
ATCCCAACGACTGCCTCCCCGACCCCTGCCACAGCCGCGGCCGCTGCTATGACCTGGTCAATGA
CTTCTACTGTGCCTGTGACGATGGCTGGAAGGGCAAGACCTGCCACTCACGCGAGTTCCAGTGT
GACGCCTACACCTGCAGCAACGGTGGCACATGCTATGACAGCGGCGACACCTTCCGCTGCGCG
TGCCCTCCGGGCTGGAAGGGCAGCACCTGCACCATCGCCAAGAACAGCAGCTGTGTGCCCAAT
CCCTGTGTGAATGGAGGCACCTGCGTGGGTAGCGGAGACTCTTTCTCCTGCATCTGCCGGGATG
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TGACTGCCGTATCAACATTGATGAGTGCCAGTCCTCGCCCTGTGCCTACGGAGCCACGTGTGTG
GATGAGATCAACGGGTACCGCTGCAGCTGCCCACCAGGTCGTTCTGGCCCCAGGTGCCAGGAA
GTGGTCATATTCACGAGGCCCTGCTGGTCCCGGGGAATGTCCTTCCCGCATGGGAGTTCCTGGA
TGGAAGACTGCAACAGCTGCCGCTGCCTGGATGGCCACCGGGATTGTAGCAAGGTATGGTGCG
GATGGAAGCCTTGCCTGCTCTCTGGTCAGCCCAGCGATCCGAGTGCCCAGTGCCCCCCAGGGCA
GCAATGTCAGGAGAAGGCCGTGGGTCAGTGCTTGCAGCCACCCTGTGAGAACTGGGGGGAGTG
TACAGCGGAGGAGCCTCTGCCACCCAGCACCCCCTGTCAGCCACGGAGCAGTCATTTGGACAA
CAACTGTGCCCGACTCACACTGCGCTTCAACCGTGATCAAGTGCCTCAGGGCACCACCGTGGGC
GCTATCTGCTCTGGAATCCGAGCCTTGCCTGCCACGAGGGCGGCGGCACACGACCGCCTCCTCC
TGCTGCTTTGTGATCGAGCATCCTCGGGGGCCAGTGCTGTGGAGGTGGCTATGTCTTTCAGCCC
TGCAAGGGACCTGCCTGACAGCAGCCTGATCCAGAGCACAGCCCACGCCATCGTGGCTGCTAT
CACTCAGAGAGGAAATAGCTCACTGCTGCTGGCTGTCACCGAGGTCAAGGTGGAAACAGTTGT
TATGGGTGGCTCTTCCACAGGTCTGTTGGTGCCCGTGCTGTGCAGCGTGTTCAGTGTGCTGTGGC
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GGCTACCACGGGATGAGAGCACCAACAACCAGTGGGCCCCGCTCAATCCCATCCGCAACCCCA
TTGAGCGGCCAGGCGGCAGCGGTCTGGGAACTGGGGGCCACAAGGACATACTCTACCAGTGCA
AAAACTTCACACCGCCGCCCCGCAGGGCAGGCGAGGCACTGCCCGGGCCAGCTGGCCATGGGG
CTGGTGGGGAGGACGAGGAGGATGAAGAGCTGAGCCGTGGAGATGGGGACTCCCCAGAGGCA
GAGAAGTTCATCTCACACAAGTTCACCAAAGACCCCAGCTGCTCCCTCGGAAGGCCAGCCTGCT
GGGCTCCAGGGCCCAAAGTGGACAACCGCGCCGTCAGAAGTACCAAGGACGTGCGCCGTGCTG
GCAGGGAGTAGCCAGCCACCAGGCTGGCACCCAGAACCCTTGCTGGCACCACGCTGCCTGCCG
GACCATAGGAGGCCAAGGCCGTGTGCATAGTTTCTTTATTTTGTGTAAAAAACAAAACCAAAAC
CAAAAAACAAATGTTTATTTTTTACGTTTCTTTAACCTTGTATAAATTATTCAACGGCTGTCAGG
CGGAAAACAACGGAGTATTCTCGGATCATTGCTATTTTTGTAAAGTTTCCGCGTCCGCACGCAC
TGTGGCAGGAGAGCAGGGCGTGTGTATGTGTGTGTGTGTGTGTCCTCACC

Figure 8

GAAGGCCATGGTCTCCCCACGGATGTCCGGGCTCCTCTCCCAGACTGTGATCCTAGCGCTCATTTTCCTC
CCCCAGACACGGCCCGCTGGCGTCTTCGAGCTGCAGATCCACTCTTTCGGGCCGGGTCCAGGCCCTGGGG
CCCCGCGGTCCCCCTGCAGCGCCCGGCTCCCCTGCCGCCTCTTCTTCAGAGTCTGCCTGAAGCCTGGGCT

CTCAGAGGAGGCCGCCGAGTCCCCGTGCGCCCTGGGCGCGGCGCTGAGTGCGCGCGGACCGGTCTACACC
GAGCAGCCCGGAGCGCCCGCGCCTGATCTCCCACTGCCCGACGGGCTCTTGCAGGTGCCCTTCCGGGACG
CCTGGCCTGGCACCTTCTCTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCAGATTGGAGGGCC
CGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGCGCTTGGCAGCCGGAGGCCCGTGGGCCCGGGC
ATTCAGCGCGCAGGCGCCTGGGAGCTGCGCTTCTCGTACCGCGCGCGCTGCGAGCCGCCTGCCGTCGGGA
CCGCGTGCACGCGCCTCTGCCGTCCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCTGCGC
ACCGCTCGAGGACGAATGTGAGGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTGT
GAACAGCCCGGTGAATGCCGATGCCTAGAGGGCTGGACTGGACCCCTCTGCACGGTCCCTGTCTCCACCA
GCAGCTGCCTCAGCCCCAGGGGCCCGTCCTCTGCTACCACCGGATGCCTTGTCCCTGGGCCTGGGCCCTG
TGACGGGAACCCGTGTGCCAATGGAGGCAGCTGTAGTGAGACACCCAGGTCCTTTGAATGCACCTGCCCG
CGTGGGTTCTACGGGCTGCGGTGTGAGGTGAGCGGGGTGACATGTGCAGATGGACCCTGCTTCAACGGCG
GCTTGTGTGTCGGGGGTGCAGACCCTGACTCTGCCTACATCTGCCACTGCCCACCTGGTTTCCAAGGCTC
CAACTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCAATGGCGGACTCTGCCTGGACCG
GGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTCGCGGGTCCTCGCTGCGAGCACGACCTGGACGACT
GCGCGGGCCGCGCCTGCGCTAACGGCGGCACGTGTGTGGAGGGCGGCGGCGCGCACCGCTGCTCCTGCC
GCTGGGCTTCGGCGGCCGCGACTGCCGCGAGCGCGCGGACCCGTGCGCCGCGCGCCCCTGTGCTCACGGC
GGCCGCTGCTACGCCCACTTCTCCGGCCTCGTCTGCGCTTGCGCTCCCGGCTACATGGGAGCGCGGTGTG
AGTTCCCAGTGCACCCCGACGGCGCAAGCGCCTTGCCCGCGGCCCCGCCGGGCCTCAGGCCCGGGGACCC
TCAGCGCTACCTTTTGCCTCCGGCTCTGGGACTGCTCGTGGCCGCGGGCGTGGCCGGCGCTGCGCTCTTG
CTGGTCCACGTGCGCCGCCGTGGCCACTCCCAGGATGCTGGGTCTCGCTTGCTGGCTGGGACCCCGGAGC
CGTCAGTCCACGCACTCCCGGATGCACTCAACAACCTAAGGACGCAGGAGGGTTCCGGGGATGGTCCGG
CTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCTCAAGGGATTTATGTCATATCTGCTCCTTCC
ATCTACGCTCGGGAGGTAGCGACGCCCCTTTTCCCCCCGCTACACACTGGGCGCGCTGGGCAGAGGCAGC
ACCTGCTTTTTCCCTACCCTTCCTCGATTCTGTCCGTGAAATGAATTGGGTAGAGTCTCTGGAAGGTTTT
AAGCCCATTTTCAGTTCTAACTTACTTTCATCCTATTTTGCATCCCTCTTATCGTTTTGAGCTACCTGCC
ATCTTCTCTTT

Figure 9

AAACCGGAACGGGGCCCAACTTCTGGGGCCTGGAGAAGGGAAACGAAGTCCCCCCCGGTTTCCCGAGGT
GCCTTTCCTCGGGCATCCTTGGTTTCGGCGGGACTTCGCAGGGCGGATATAAAGAACGGCGCCTTTGGGA
AGAGGCGGAGACCGGCTTTAAAGAAAGAAGTCTTGGTCCTGCGGCTTGGGCGAGGCAAGGGCGAGGCAG
GGCGCTTTCTGCCGACGCTCCCCGTGGCCCTACGATCCCCGCGCGTCCGCCGCTGTTCTAAGGAGAGAA
GTGGGGGCCCCCCAGGCTCGCGCGTGGAGCGAAGCAGCATGGGCAGTCGGTGCGCGCTGGCCCTGGCGT
GCTCTCGGCCTTGCTGTGTCAGGTCTGGAGCTCTGGGGTGTTCGAACTGAAGCTGCAGGAGTTCGTCAAC
AAGAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCGCGGGGCCACCGCCGTGCGCCTGCCGA
CCTTCTTCCGCGTGTGCCTCAAGCACTACCAGGCCAGCGTGTCCCCCGAGCCGCCCTGCACCTACGGCAG
CGCCGTCACCCCCGTGCTGGGCGTCGACTCCTTCAGTCTGCCCGACGGCGGGGGCGCCGACTCCGCGTTC
AGCAACCCCATCCGCTTCCCCTTCGGCTTCACCTGGCCGGGCACCTTCTCTCTGATTATTGAAGCTCTCC
ACACAGATTCTCCTGATGACCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCTGGCCACCCAGAG
GCACCTGACGGTGGGCGAGGAGTGGTCCCAGGACCTGCACAGCAGCGGCCGCACGGACCTCAAGTACTC
TACCGCTTCGTGTGTGACGAACACTACTACGGAGAGGGCTGCTCCGTTTTCTGCCGTCCCCGGGACGATG
CCTTCGGCCACTTCACCTGTGGGGAGCGTGGGGAGAAAGTGTGCAACCCTGGCTGGAAAGGGCCCTACTG
CACAGAGCCGATCTGCCTGCCTGGATGTGATGAGCAGCATGGATTTTGTGACAAACCAGGGGAATGCAAG
TGCAGAGTGGGCTGGCAGGGCCGGTACTGTGACGAGTGTATCCGCTATCCAGGCTGTCTCCATGGCACCT
GCCAGCAGCCCTGGCAGTGCAACTGCCAGGAAGGCTGGGGGGGCCTTTTCTGCAACCAGGACCTGAACTA
CTGCACACACCATAAGCCCTGCAAGAATGGAGCCACCTGCACCAACACGGGCCAGGGGAGCTACACTTC
TCTTGCCGGCCTGGGTACACAGGTGCCACCTGCGAGCTGGGGATTGACGAGTGTGACCCCAGCCCTTGTA
AGAACGGAGGGAGCTGCACGGATCTCGAGAACAGCTACTCCTGTACCTGCCCACCCGGCTTCTACGGCAA
AATCTGTGAATTGAGTGCCATGACCTGTGCGGACGGCCCTTGCTTTAACGGGGGTCGGTGCTCAGACAGC
CCCGATGGAGGGTACAGCTGCCGCTGCCCCGTGGGCTACTCCGGCTTCAACTGTGAGAAGAAAATTGACT
ACTGCAGCTCTTCACCCTGTTCTAATGGTGCCAAGTGTGTGGACCTCGGTGATGCCTACCTGTGCCGCTG
CCAGGCCGGCTTCTCGGGGAGGCACTGTGACGACAACGTGGACGACTGCGCCTCCTCCCCGTGCGCCAAC
GGGGGCACCTGCCGGGATGGCGTGAACGACTTCTCCTGCACCTGCCCGCCTGGCTACACGGGCAGGAACT
GCAGTGCCCCCGTCAGCAGGTGCGAGCACGCACCCTGCCACAATGGGGCCACCTGCCACCAGAGGGGCA
CGGCTATGTGTGCGAATGTGCCCGAAGCTACGGGGGTCCCAACTGCCAGTTCCTGCTCCCCGAGCTGCCC
CCGGGCCCAGCGGTGGTGGACCTCACTGAGAAGCTAGAGGGCCAGGGCGGGCCATTCCCCTGGGTGGCG
TGTGCGCCGGGGTCATCCTTGTCCTCATGCTGCTGCTGGGCTGTGCCGCTGTGGTGGTCTGCGTCCGGCT
GAGGCTGCAGAAGCACCGGCCCCCAGCCGACCCCTGCCGGGGGGAGACGGAGACCATGAACAACCTGGC
AACTGCCAGCGTGAGAAGGACATCTCAGTCAGCATCATCGGGGCCACGCAGATCAAGAACACCAACAAA
AGGCGGACTTCCACGGGGACCACAGCGCCGACAAGAATGGCTTCAAGGCCCGCTACCCAGCGGTGGACA
TAACCTCGTGCAGGACCTCAAGGGTGACGACACCGCCGTCAGGGACGCGCACAGCAAGCGTGACACCAG

TGCCAGCCCCAGGGCTCCTCAGGGGAGGAGAAGGGGACCCCGACCACACTCAGGGGTGGAGAAGCATCG
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CGAGGAGAAGGATGAGTGCGTCATAGCAACTGAGGTGTAAAATGGAAGTGAGATGGCAAGACTCCCGTT
CTCTTAAAATAAGTAAAATTCCAAGGATATATGCCCCAACGAATGCTGCTGAAGAGGAGGGAGGCCTCGT
GGACTGCTGCTGAGAAACCGAGTTCAGACCGAGCAGGTTCTCCTCCTGAGGTCCTCGACGCCTGCCGACA
GCCTGTCGCGGCCCGGCCGCCTGCGGCACTGCCTTCCGTGACGTCGCCGTTGCACTATGGACAGTTGCTC
TTAAGAGAATATATATTTAAATGGGTGAACTGAATTACGCCTAAGAAGCATGCACTGCCTGAGTGTATAT
TTTGGATTCTTATGAGCCAGTCTTTTCTTGAATTAGAAACACAAACACTGCCTTTATTGTCCTTTTTGAT
ACGAAGATGTGCTTTTTCTAGATGGAAAAGATGTGTGTTATTTTTTGGATTTGTAAAAATATTTTTCATG
ATATCTGTAAAGCTTGAGTATTTTGTGATGTTCGTTTTTTATAATTTAAATTTTGGTAAATATGTACAAA
GGCACTTCGGGTCTATGTGACTATATTTTTTTGTATATAAATGTATTTATGGAATATTGTGCCAATGTTA
TTTGAGTTTTTTACTGTTTTGTTAATGAAGAAATTCCTTTTTAAAATATTTTTCCAAAATAAATTTTATG
AGGAATTC

Figure 10

ATGGCGGCAGCGTCCCGGAGCGCCTCTGGCTGGGCGCTACTGCTGCTGGTGGCACTTTGGCAGCAGCGCG
CGGCCGGCTCCGGCGTCTTCCAGCTGCAGCTGCAGGAGTTCATCAACGAGCGCGGCGTACTGGCCAGTGG
GCGGCCTTGCGAGCCCGGCTGCCGGACTTTCTTCCGCGTCTGCCTTAAGCACTTCCAGGCGGTCGTCTCG
CCCGGACCCTGCACCTTCGGGACCGTCTCCACGCCGGTATTGGGCACCAACTCCTTCGCTGTCCGGGACG
ACAGTAGCGGCGGGGGGCGCAACCCTCTCCAACTGCCCTTCAATTTCACCTGGCCGGGTACCTTCTCGCT
CATCATCGAAGCTTGGCACGCGCCAGGAGACGACCTGCGGCCAGAGGCCTTGCCACCAGATGCACTCATC
AGCAAGATCGCCATCCAGGGCTCCCTAGCTGTGGGTCAGAACTGGTTATTGGATGAGCAAACCAGCACCC
TCACAAGGCTGCGCTACTCTTACCGGGTCATCTGCAGTGACAACTACTATGGAGACAACTGCTCCCGCCT
GTGCAAGAAGCGCAATGACCACTTCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCCTGCCTGCCC
GGTTGGACTGGGGAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTCATGAACAGAATGGCTACTGCA
GCAAGCCAGCAGAGTGCCTCTGCCGCCCAGGCTGGCAGGGCCGGCTGTGTAACGAATGCATCCCCCACAA
TGGCTGTCGCCACGGCACCTGCAGCACTCCCTGGCAATGTACTTGTGATGAGGGCTGGGGAGGCCTGTTT
TGTGACCAAGATCTCAACTACTGCACCCACCACTCCCCATGCAAGAATGGGGCAACGTGCTCCAACAGTG
GGCAGCGAAGCTACACCTGCACCTGTCGCCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGA
GTGTGACAGCAACCCCTGTCGCAATGGAGGCAGCTGTAAGGACCAGGAGGATGGCTACCACTGCCTGTGT
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GGGGCTCCTGCCGGGAGCGCAACCAGGGGGCCAACTATGCTTGTGAATGTCCCCCCAACTTCACCGGCTC
CAACTGCGAGAAGAAAGTGGACAGGTGCACCAGCAACCCCTGTGCCAACGGGGGACAGTGCCTGAACCA
GGTCCAAGCCGCATGTGCCGCTGCCGTCCTGGATTCACGGGCACCTACTGTGAACTCCACGTCAGCGACT
GTGCCCGTAACCCTTGCGCCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTGCACCTGCCC
TGCCGGCTTCTCTGGCCGACGCTGTGAGGTGCGGACATCCATCGATGCCTGTGCCTCGAGTCCCTGCTTC
AACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTGTGCAACTGCCCTTATGGCTTTGTGG
GCAGCCGCTGCGAGTTCCCCGTGGGCTTGCCGCCCAGCTTCCCCTGGGTGGCCGTCTCGCTGGGTGTGGG
GCTGGCAGTGCTGCTGGTACTGCTGGGCATGGTGGCAGTGGCTGTGCGGCAGCTGCGGCTTCGACGGCCG
GACGACGGCAGCAGGGAAGCCATGAACAACTTGTCGGACTTCCAGAAGGACAACCTGATTCCTGCCGCC
AGCTTAAAAACACAAACCAGAAGAAGGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCAACTGTGGCA
ACAGCAAAACCACACATTGGACTATAATCTGGCCCCAGGGCCCCTGGGGCGGGGACCATGCCAGGAAG
TTTCCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGCCACTGCGGTTACACAGTGAAAAGCCAGAGTGC
GGATATCAGCGATATGCTCCCCCAGGGACTCCATGTACCAGTCTGTGTGTTTGATATCAGAGGAGAGGAA
TGAATGTGTCATTGCCACGGAGGTATAA

Figure 11

CTCGCAGGCTAGGAACCCGAGGCCAAGAGCTGCAGCCAAAGTCACTTGGGTGCAGTGTACTCCCTCACTA
GCCCGCTCGAGACCCTAGGATTTGCTCCAGGACACGTACTTAGAGCAGCCACCGCCCAGTCGCCCTCACC
TGGATTACCTACCGAGGCATCGAGCAGCGGAGTTTTTGAGAAGGCGACAAGGGAGCAGCGTCCCGAGGG
AATCAGCTTTTCAGGAACTCGGCTGGCAGACGGGACTTGCGGGAGAGCGACATCCCTAACAAGCAGATTC
GGAGTCCCGGAGTGGAGAGGACACCCCAAGGGATGACGCCTGCGTCCCGGAGCGCCTGTCGCTGGGCGT
ACTGCTGCTGGCGGTACTGTGGCCGCAGCAGCGCGCTGCGGGCTCCGGCATCTTCCAGCTGCGGCTGCAG
GAGTTCGTCAACCAGCGCGGTATGCTGGCCAATGGGCAGTCCTGCGAACCGGGCTGCCGGACTTTCTTCC
GCATTTGCCTTAAGCACTTCCAGGCAACCTTCTCCGAGGGACCCTGCACCTTTGGCAATGTCTCCACGCC
GGTATTGGGCACCAACTCCTTCGTCGTCAGGGACAAGAATAGCGGCAGTGGTCGCAACCCTCTGCAGTTG
CCCTTCAATTTCACCTGGCCGGGAACCTTCTCACTCAACATCCAAGCTTGGCACACACCGGGAGACGACC
TGCGGCCAGAGACTTCGCCAGGAAACTCTCTCATCAGCCAAATCATCATCCAAGGCTCTCTTGCTGTGGG

TAAGATTTGGCGAACAGACGAGCAAAATGACACCCTCACCAGACTGAGCTACTCTTACCGGGTCATCTGC
AGTGACAACTACTATGGAGAGAGCTGTTCTCGCCTATGCAAGAAGCGCGATGACCACTTCGGACATTATG
AGTGCCAGCCAGATGGCAGCCTGTCCTGCCTGCCGGGCTGGACTGGGAAGTACTGTGACCAGCCTATATG
TCTTTCTGGCTGTCATGAGCAGAATGGTTACTGCAGCAAGCCAGATGAGTGCATCTGCCGTCCAGGTTGG
CAGGGTCGCCTGTGCAATGAATGTATCCCCCACAATGGCTGTCGTCATGGCACCTGCAGCATCCCCTGGC
AGTGTGCCTGCGATGAGGGATGGGGAGGTCTGTTTTGTGACCAAGATCTCAACTACTGTACTCACCACTC
TCCGTGCAAGAATGGATCAACGTGTTCCAACAGTGGGCCAAAGGGTTATACCTGCACCTGTCTCCCAGGC
TACACTGGTGAGCACTGTGAGCTGGGACTCAGCAAGTGTGCCAGCAACCCCTGTCGAAATGGTGGCAGCT
GTAAGGACCAGGAGAATAGCTACCACTGCCTGTGTCCCCCAGGCTACTATGGCCAGCACTGTGAGCATAG
TACCTTGACCTGTGCGGACTCACCCTGCTTCAATGGGGGCTCTTGCCGGGAGCGCAACCAGGGGTCCAGT
TATGCCTGCGAATGCCCCCCCAACTTTACCGGCTCTAACTGTGAGAAGAAAGTAGACAGGTGTACCAGCA
ACCCGTGTGCCAATGGAGGCCAGTGCCTGAACAGAGGTCCAAGCCGAACCTGCCGCTGCCGGCCTGGATT
CACAGGCACCCACTGTGAACTGCACATCAGCGATTGTGCCCGAAGTCCCTGTGCCCACGGGGGCACTTGC
CACGATCTGGAGAATGGGCCTGTGTGCACCTGCCCCGCTGGCTTCTCTGGCAGGCGCTGCGAGGTGCGGA
TAACCCACGATGCCTGTGCCTCCGGACCCTGCTTCAATGGGGCCACCTGCTACACTGGCCTCTCCCCAAA
CAACTTCGTCTGCAACTGTCCTTATGGCTTTGTGGGCAGCCGCTGCGAGTTTCCCGTGGGCTTGCCACCC
AGCTTCCCCTGGGTAGCTGTCTCGCTGGGCGTGGGGCTAGTGGTACTGCTGGTGCTGCTGGTCATGGTGG
TAGTGGCTGTGCGGCAGCTGCGGCTTCGGAGGCCCGATGACGAGAGCAGGGAAGCCATGAACAATCTGC
AGACTTCCAGAAGGACAACCTAATCCCTGCCGCCCAGCTCAAAAACACAAACCAGAAGAAGGAGCTGGA
GTGGACTGTGGTCTGGACAAGTCCAATTGTGGCAAACTGCAGAACCACACATTGGACTACAATCTAGCCC
CGGGACTCCTAGGACGGGGCAGCATGCCTGGGAAGTATCCTCACAGTGACAAGAGCTTAGGAGAGAAGT
GCCACTTCGGTTACACAGTGAGAAGCCAGAGTGTCGAATATCAGCCATTTGCTCTCCCAGGGACTCTATG
TACCAATCAGTGTGTTTGATATCAGAAGAGAGGAACGAGTGTGTGATTGCCACAGAGGTATAAGGCAGA
GCCTACTCAGACACCCAGCTCCGGCCCAGCAGCTGGGCCTTCCTTCTGCATTGTTTACATTGCATCCTGT
ATGGGACATCTTTAGTATGCACAGTGCTGCTCTGCGGAGGAGGAGGGAATGGCATGAACTGAACAGACG
TGAACCCGCCAAGAGTTGCACCGGCTCTGCACACCTCCAGGAGTCTGCCTGGCTTCAGATGGGCAGCCCC
GCCAAGGGAACAGAGTTGAGGAGTTAGAGGAGCATCAGTTGAGCTGATATCTAAGGTGCCTCTCGAACTT
GGACTTGCTCTGCCAACAGTGGTCATCATGGAGCTCTTGACTGTTCTCCAGAGAGTGGCAGTGGCCCTAG
TGGGTCTTGGCGCTGCTGTAGCTCCTGTGGGCATCTGTATTTCCAAAGTGCCTTTGCCCAGACTCCATCC
TCACAGCTGGGCCCAAATGAGAAAGCAGAGAGGAGGCTTGCAAAGGATAGGCCTCCCGCAGGCAGAACG
CCTTGGAGTTTGGCATTAAGCAGGAGCTACTCTGCAGGTGAGGAAAGCCCGAGGAGGGGACACGTGTGC
TCCTGCCTCCAACCCCAGCAGGTGGGGTGCCACCTGCAGCCTCTAGGCAAGAGTTGGTCCTTCCCCTGGT
CCTGGTGCCTCTGGGCTCATGTGAACAGATGGGCTTAGGGCACGCCCCTTTTGCCAGCCAGGGGTACAGG
CCTCACTGGGGAGCTCAGGGCCTTCATGCTAAACTCCCAATAAGGGAGATGGGGGAAGGGGGCTGTGC
CTAGGCCCTTCCCTCCCTCACACCCATTTTTGGGCCCTTGAGCCTGGGCTCCACCAGTGCCCACTGTTGC
CCCGAGACCAACCTTGAAGCCGATTTCAAAAATCAATAATATGAGGTTTTGTTTTGTAGTTTATTTTGG
AATCTAGTATTTTGATAATTTAAGAATCAGAAGCACTGGCCTTTCTACATTTTATAACATTATTTTGTAT
ATAATGTGTATTTATAATATGAAACAGATGTGTACATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Figure 12

AAACCCACTCCACCTTACTACCAGACAACCTTAGCCAAACCATTTACCCAAATAAAGTATAGGC
GATAGAAATTGAAACCTGGCGCAATAGATATAGTACCGCAAGGGAAAGATGAAAAATTATAAC
CAAGCATAATATAGCAAGGACTAACCCCTATACCTTCTGCATAATGAATTAACTAGAAATAACT
TTGCAAGGAGAGTCAAAGCTAAGGCCCCCGAAACCAGGCGAGCTACCTAAGAACAGCTAAAA
GAGCACACCCGTCTATGTAGCAAAATAGTGGGAAGATTTATAGGTAGAGGCGACAAACCTACC
GAGCCTGGTGATAGCTGGTTGTCCAAGATAGAATCTTAGTTCAACTTTAAATTTGCCCACAGAA
CCCTCTAAATCCCCTTGTAAATTTAACTGTTAGTCCAAAGAGGAACAGCTCTTTGGACACTAGG
AAAAAACCTTGTAGAGAGAGTGTCAGCCCAATTCCACACTTTTCCACATGTTGGATGGCCTTGG
AGTGGTAGCCATAAGCATTTTTGGAATTCAACTAAAAACTGAAGGATCCTTGAGGACGGCAGT
ACCTGGCATACCTACACAGTCAGCGTTCAACAAGTGTTTGCAAAGGTACATTGGGGCACTGGG
GGCACGAGTGATCTGTGACAATATCCCTGGTTTGGTGAGCCGGCAGCGGCAGCTGTGCCAGCGT
TACCCAGACATCATGCGTTCAGTGGGCGAGGGTGCCCGAGAATGGATCCGAGAGTGTCAGCAC
CAATTCCGCCACCACCGCTGGAACTGTACCACCCTGGACCGGGACCACACCGTCTTTGGCCGTG
TCATGCTCAGAAGTAGCCGAGAGGCAGCTTTTGTATATGCCATCTCATCAGCAGGGGTGATCCA
CGCTATTACTCGCGCCTGTAGCCAGGGTGAACTGAGTGTGTGCAGCTGTGACCCCTACACCCGT
GGCCGACACCATGACCAGCGTGGGACTTTTGACTGGGGTGGCTGCAGTGACAACATCCACTAC
GGTGTCCGTTTTGCCAAGGCCTTCGTGGATGCCAAGGAGAAGAGGCTTAAGGATGCCCGGGCC
CTCATGAACTTACATAATAACCGCTGTGGTCGCACGGCTGTGCGGCGGTTTGTCAAGCTGGAGT

GTAAGTGCCATGGCGTGAGTGGTTCCTGTACTCTGCGCACCTGCTGGCGTGCACTCTCAGATTT
CCGCCGCACAGGTGATTACCTGCGGCGACGCTATGATGGGGCTGTGCAGGTGATGGCCACCCA
AGATGGTGCCAACTTCACCGCAGCCCGCCAAGGCTATCGCCGTGCCACCCGGAGTGATCTTGTC
TACTTTGACAACTCTCCAGATTACTGTGTCTTGGACAAGGCTGCAGGTTCCCTAGGCACTGCAG
GCCGTGTCTGCAGCAAGACATCAAAAGGAACAGACGGTTGTGAAATCATGTGCTGTGGCCGAG
GGTACGACACAACTCGAGTCACCCGTGTTACCCAGTGTGAGTGCAAATTCCACTGGTGCTGTGC
TGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTCCATACTTGCAAAGCCCCCAAGAAGGC
AGAGTGGCTGGACCAGACCTGAACACACAGATACCTCACTCATCCCTCCAATTCAAGCCTCTCA
ACTCAAAAGCACAAGATCCTTGCATGCACACCTTCCTCCACCCTCCACCCTGGGCTGCTACCGC
TTCTATTTAAGGATGTAGAGAGTAATCCATAGGGACCATGGTGTCCTGGCTGGTTCCTTAGCCC
TGGGAAGGAGTTGTCAGGGGATATAAGAAACTGTGCAAGCTCCCTGATTTCCCGCTCTGGAGAT
TTGAAGGGAGAGTAGAAGAGATAGGGGGTCTTTAGAGTGAAATGAGTTGCACTAAAGTACGTA
GTTGAGGCTCCTTTTTTCTTTCCTTTGCACCAGCTTCCCGACACTTCTTGGTGTGCAAGAGGAAG
GGTACCTGTAGAGAGCTTCTTTTTGTTTCTACCTGGCCAAAGTTAGATGGGACAAAGATGAATG
GCATGTCCCTTCTCTGAAGTCCGTTTGAGCAGAACTACCTGGTACCCCGAAAGAAAAATCTTAG
GCTACCACATTCTATTATTGAGAGCCTGAGATGTTAGCCATAGTGGACAAGGTTCCATTCACAT
GCTCATATGTTTATAAACTGTGTTTTGTAGAAGAAAAAGAATCATAACAATACAAACACACATT
CATTCTCTCTTTTTCTCTCTACCATTCTCAACCTGTATTGGACAGCACTGCCTCTTTTGCTTACTT
GCTGCCTGTTCAAACTGAGGTGGAATGCAGTGGTTCCCATGCTTAACAGATCATTAAAACACCC
TAGAACACTCCTAGGATAGATTAATGT

Figure 13

ACCGCAGGGGGCTCCCGGACCCTGACTCTGCAGCCGAACCGGCACGGTTTCGTGGGGACCCAG
GCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCTCCCTCTTGAGTCCTTCTGAGATGATGGCTCT
GGGCGCAGCGGGAGCTACCCGGGTCTTTGTCGCGATGGTAGCGGCGGCTCTCGGCGGCCACCC
TCTGCTGGGAGTGAGCGCCACCTTGAACTCGGTTCTCAATTCCAACGCTATCAAGAACCTGCCC
CCACCGCTGGGCGGCGCTGCGGGGCACCCAGGCTCTGCAGTCAGCGCCGCGCCGGGAATCCTG
TACCCGGGCGGGAATAAGTACCAGACCATTGACAACTACCAGCCGTACCCGTGCGCAGAGGAC
GAGGAGTGCGGCACTGATGAGTACTGCGCTAGTCCCACCCGCGGAGGGGACGCAGGCGTGCAA
ATCTGTCTCGCCTGCAGGAAGCGCCGAAAACGCTGCATGCGTCACGCTATGTGCTGCCCCGGGA
ATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAAATCATTTCCGAGGAGAAATTGAGGA
AACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTTGGATGGGTATTCCAGAAGAACCACC
TTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTGTTTGTCTCCGGTCATCAGACT
GTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCAAGATCTGTAAACCTGTCCTGAAAGA
AGGTCAAGTGTGTACCAAGCATAGGAGAAAAGGCTCTCATGGACTAGAAATATTCCAGCGTTG
TTACTGTGGAGAAGGTCTGTCTTGCCGGATACAGAAAGATCACCATCAAGCCAGTAATTCTTCT
AGGCTTCACACTTGTCAGAGACACTAAACCAGCTATCCAAATGCAGTGAACTCCTTTTATATAA
TAGATGCTATGAAAACCTTTTATGACCTTCATCAACTCAATCCTAAGGATATACAAGTTCTGTG
GTTTCAGTTAAGCATTCCAATAACACCTTCCAAAAACCTGGAGTGTAAGAGCTTTGTTTCTTTAT
GGAACTCCCCTGTGATTGCAGTAAATTACTGTATTGTAAATTCTCAGTGTGGCACTTACCTGTAA
ATGCAATGAAACTTTTAATTATTTTTCTAAAGGTGCTGCACTGCCTATTTTTCCTCTTGTTATGTA
AATTTTTGTACACATTGATTGTTATCTTGACTGACAAATATTCTATATTGAACTGAAGTAAATCA
TTTCAGCTTATAGTTCTTAAAAGCATAACCCTTTACCCCATTTAATTCTAGAGTCTAGAACGCAA
GGATCTCTTGGAATGACAAATGATAGGTACCTAAAATGTAACATGAAAATACTAGCTTATTTTC
TGAAATGTACTATCTTAATGCTTAAATTATATTTCCCTTTAGGCTGTGATAGTTTTGAAATAAA
ATTTAACATTTAATATCATGAAATGTTATAA

Figure 14

AGAAAGCGGGAGCCCGCGGCGAGCGTAGCGCAAGTCCGCTCCCTAGGCATCGCTGCGCTGGCA
GCGATTCGCTGTCTCTTGTGAGTCAGGGGACAACGCTTCGGGGCAACTGTGAGTGCGCGTGTGG
GGGACCTCGATTCTCTTCAGATCTCGAGGATTCGGTCCGGGGACGTCTCCTGATCCCCTACTAA

AGCGCCTGCTAACTTTGAAAAGGAGCACTGTGTCCTGCAAAGTTTGACACATAAAGGATAGGA
AAAGAGAGGAGAGAAAAGCAACTGAGTTGAAGGAGAAGGAGCTGATGCGGGCCTCCTGATCA
ATTAAGAGGAGAGTTAAACCGCCGAGATCCCGGCGGGACCAAGGAGGTGCGGGGCAAGAAGG
AACGGAAGCGGTGCGATCCACAGGGCTGGGTTTTCTTGCACCTTGGGTCACGCCTCCTTGGCGA
GAAAGCGCCTCGCATTTGATTGCTTCCAGTTATTGCAGAACTTCCTGTCCTGGTGGAGAAGCGG
GTCTCGCTTGGGTTCCGCTAATTTCTGTCCTGAGGCGTGAGACTGAGTTCATAGGGTCCTGGGTC
CCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGCGACCCAAGTGAGGGGCCC
CGTGTTGGGGTCCTCCCTCCCTTTGCATTCCCACCCCTCCGGGCTTTGCGTCTTCCTGGGGACCC
CCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGGATTCGTCCTGCTGCCTGCTCCTACTGG
CCGCGGTGCTGATGGTGGAGAGCTCACAGATCGGCAGTTCGCGGGCCAAACTCAACTCCATCA
AGTCCTCTCTGGGCGGGGAGACGCCTGGTCAGGCCGCCAATCGATCTGCGGGCATGTACCAAG
GACTGGCATTCGGCGGCAGTAAGAAGGGCAAAAACCTGGGGCAGGCCTACCCTTGTAGCAGTG
ATAAGGAGTGTGAAGTTGGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGCATGG
TGTGTCGGAGAAAAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGCTGCA
ATAATGGCATCTGTATCCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGGATGG
TACTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGAATCT
AGGAAGACCACACACTAAGATGTCACATATAAAAGGGCATGAAGGAGACCCCTGCCTACGATC
ATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCAAAATCTGCAAACCAGTG
CTCCATCAGGGGGAAGTCTGTACCAAACAACGCAAGAAGGGTTCTCATGGGCTGGAAATTTTC
CAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATGGAAAGATGCCACCTACTCCTCCA
AAGCCAGACTCCATGTGTGTCAGAAAATTTGATCACCATTGAGGAACATCATCAATTGCAGACT
GTGAAGTTGTGTATTTAATGCATTATAGCATGGTGGAAAATAAGGTTCAGATGCAGAAGAATG
GCTAAAATAAGAAACGTGATAAGAATATAGATGATCACAAAAAGGGAGAAAGAAAACATGAA
CTGAATAGATTAGAATGGGTGACAAATGCAGTGCAGCCAGTGTTTCCATTATGCAACTTGTCTA
TGTAAATAATGTACACATTTGTGGAAAATGCTATTATTAAGAGAACAAGCACACAGTGGAAAT
TACTGATGAGTAGCATGTGACTTTCCAAGAGTTTAGGTTGTGCTGGAGGAGAGGTTTCCTTCAG
ATTGCTGATTGCTTATACAAATAACCTACATGCCAGATTTCTATTCAACGTTAGAGTTTAACAA
AATACTCCTAGAATAACTTGTTATACAATAGGTTCTAAAAATAAAATTGCTAAACAAGAAATGA
AAACATGGAGCATTGTTAATTTACAACAGAAAATTACCTTTTGATTTGTAACACTACTTCTGCTG
TTCAATCAAGAGTCTTGGTAGATAAGAAAAAAATCAGTCAATATTTCCAAATAATTGCAAAATA
ATGGCCAGTTGTTTAGGAAGGCCTTTAGGAAGACAAATAAATAACAAACAAACAGCCACAAAT
ACTTTTTTTTCAAAATTTAGTTTTACCTGTAATTAATAAGAACTGATACAAGACAAAAACAGTT
CCTTCAGATTCTACGGAATGACAGTATATCTCTCTTTATCCTATGTGATTCCTGCTCTGAATGCA
TTATATTTTCCAAACTATACCCATAAATTGTGACTAGTAAAATACTTACACAGAGCAGAATTTT
CACAGATGGCAAAAAAATTTAAAGATGTCCAATATATGTGGAAAAGAGCTAACAGAGAGATC
ATTATTTCTTAAAGATTGGCCATAACCTGTATTTTGATAGAATTAGATTGGTAAATACATGTATT
CATACATACTCTGTGGTAATAGAGACTTGAGCTGGATCTGTACTGCACTGGAGTAAGCAAGAA
AATTGGGAAAACTTTTTCGTTTGTTCAGGTTTTGGCAACACATAGATCATATGTCTGAGGCACA
AGTTGGCTGTTCATCTTTGAAACCAGGGGATGCACAGTCTAAATGAATATCTGCATGGGATTTG
CTATCATAATATTTACTATGCAGATGAATTCAGTGTGAGGTCCTGTGTCCGTACTATCCTCAAAT
TATTTATTTTATAGTGCTGAGATCCTCAAATAATCTCAATTTCAGGAGGTTTCACAAAATGGACT
CCTGAAGTAGACAGAGTAGTGAGGTTTCATTGCCCTCTATAAGCTTCTGACTAGCCAATGGCAT
CATCCAATTTTCTTCCCAAACCTCTGCAGCATCTGCTTTATTGCCAAAGGGCTAGTTTCGGTTTT
CTGCAGCCATTGCGGTTAAAAAATATAAGTAGGATAACTTGTAAAACCTGCATATTGCTAATCT
ATAGACACCACAGTTTCTAAATTCTTTGAAACCACTTTACTACTTTTTTTAAACTTAACTCAGTT
CTAAATACTTTGTCTGGAGCACAAAACAATAAAAGGTTATCTTATAGTCGTGACTTTAAACTTT
TGTAGACCACAATTCACTTTTTAGTTTTCTTTTACTTAAATCCCATCTGCAGTCTCAAATTTAAGT
TCTCCCAGTAGAGATTGAGTTTGAGCCTGTATATCTATTAAAAATTTCAACTTCCCACATATATT
TACTAAGATGATTAAGACTTACATTTTCTGCACAGGTCTGCAAAAACAAAAATTATAAACTAGT
CCATCCAAGAACCAAAGTTTGTATAAACAGGTTGCTATAAGCTTGGTGAAATGAAAATGGAAC
ATTTCAATCAAACATTTCCTATATAACAATTATTATATTTACAATTTGGTTTCTGCAATATTTTTC
TTATGTCCACCCTTTTAAAAATTATTATTTGAAGTAATTTATTTACAGGAAATGTTAATGAGATG
TATTTTCTTATAGAGATATTTCTTACAGAAAGCTTTGTAGCAGAATATATTTGCAGCTATTGACT
TTGTAATTTAGGAAAAATGTATAATAAGATAAAATCTATTAAATTTTTCTCCTCTAAAAACTGA
ATTCAAAGC

Figure 15

ACACACAGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCTGCTGTG
CCTGCTGCTGGCGGCGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCGACCTCGGCTCCA
GTCAAGCCCGGCCCGGCTCTCAGCTACCCGCAGGAGGAGGCCACCCTCAATGAGATGTTCCGC
GAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGGAAGAGATGGA
GGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAGTGAACCTGGCAAACTTACCTCCCAGCTA
TCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCACCGAGAAAT
TCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAGTTATCACATCTGTG
GGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCCAGCAT
GTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTCTGC
ACCCGGGACAGTGAGTGCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATGGCC
ACCAGGGGCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGT
GCCTTCCAGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCC
ATGACCCCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGA
CCGATGCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGC
AAGCCGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCC
GATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGG
AGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGAGGG
GAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCC
CCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTACATCTTCTTCCCAGTAAGTTTC
CCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTCAGCTCCCCCAGGCTGTTCTCCAGGCT
TCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACCCCTGT
CCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTTCTACATGGCTTTGAT
AATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGGGAAATG
TGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATTTTCCA
CGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTTCTGTTC
ACCCTGCATTACATGTGTTTATTCATCCAGCAGTGTTGCTCAGCTCCTACCTCTGTGCCAGGGCA
GCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCACAGCCTGGGGAGGGGGTCATTGTTCTCC
TCGTCCATCAGGGATCTCAGAGGCTCAGAGACTGCAAGCTGCTTGCCCAAGTCACACAGCTAGT
GAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCCACAC
CAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTTTGAGGCA
TGCACATCTGGAATTAAGGTCAAACTAATTCTCACATCCCTCTAAAAGTAAACTACTGTTAGGA
ACAGCAGTGTTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTGACACTGT
CCCTCTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATACAGGTTAA
CCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAATCAC
TTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGGCTGTGTG
AAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAATGATGTTTTC
AGGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAAAGTTTAAAGTTGCACATG
ATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACATAAGTTGCATTTAGAAATCA
AGCATAAATCACTTCAACTGCTCTTCT

Figure 16

GACAAACAGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGC
CTCGCTTTGGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTGGCG
GCCGTCCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGGTCCTGGACTTCAACA
ACATCAGGAGCTCTGCTGACCTGCATGGGGCCCGGAAGGGCTCACAGTGCCTGTCTGACACGG
ACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGCCGTTCTGTGCTACATGTCG
TGGGTTGCGGAGGAGGTGCCAGCGAGATGCCATGTGCTGCCCTGGGACACTCTGTGTGAACGA
TGTTTGTACTACGATGGAAGATGCAACCCCAATATTAGAAAGGCAGCTTGATGAGCAAGATGG
CACACATGCAGAAGGAACAACTGGGCACCCAGTCCAGGAAAACCAACCCAAAAGGAAGCCAA
GTATTAAGAAATCACAAGGCAGGAAGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTGACT
GTGGCCCTGGACTTTGCTGTGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAG
GGACAGGTCTGCTCCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGT

TGCGACTGTGGCCCTGGACTACTGTGTCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGAT
TAAGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAATCCACATTGC
ATTTGAG

Figure 17

ATGGGGCTCTGGGCGCTGTTGCCTGGCTGGGTTTCTGCTACGCTGCTGCTGGCGCTGGCCGCTCT
GCCCGCAGCCCTGGCTGCCAACAGCAGTGGCCGATGGTGGGGTATTGTGAACGTAGCCTCCTCC
ACGAACCTGCTTACAGACTCCAAGAGTCTGCAACTGGTACTCGAGCCCAGTCTGCAGCTGTTGA
GCCGCAAACAGCGGCGCCTGATACGCCAAAATCCGGGATCCTGCACAGCGTGAGTGGGGGGC
TGCAGAGTGCCGTGCGCGAGTGCAAGTGGCAGTTCCGGAATCGCCGCTGGAACTGTCCCACTG
CTCCAGGGCCCCACCTCTTCGGCAAGATCGTCAACCGAGGCTGTCGAGAAACGGCGTTTATCTT
CGCTATCACCTCCGCCGGGGTCACCCATTCGGTGGCGCGCTCCTGCTCAGAAGGTTCCATCGAA
TCCTGCACGTGTGACTACCGGCGGCGCGGCCCCGGGGGCCCCGACTGGCACTGGGGGGGCTGC
AGCGACAACATTGACTTCGGCCGCCTCTTCGGCCGGGAGTTCGTGGACTCCGGGGAGAAGGGG
CGGGACCTGCGCTTCCTCATGAACCTTCACAACAACGAGGCAGGCCGTACGACCGTATTCTCCG
AGATGCGCCAGGAGTGCAAGTGCCACGGGATGTCCGGCTCATGCACGGTGCGCACGTGCTGGA
TGCGGCTGCCCACGCTGCGCGCCGTGGGCGATGTGCTGCGCGACCGCTTCGACGGCGCCTCGCG
CGTCCTGTACGGCAACCGCGGCAGCAACCGCGCTTCGCGAGCGGAGCTGCTGCGCCTGGAGCC
GGAAGACCCGGCCCACAAACCGCCCTCCCCCCACGACCTCGTCTACTTCGAGAAATCGCCCAAC
TTCTGCACGTACAGCGGACGCCTGGGCACAGCAGGCACGGCAGGGCGCGCCTGTAACAGCTCG
TCGCCCGCGCTGGACGGCTGCGAGCTGCTCTGCTGCGGCAGGGGCCACCGCACGCGCACGCAG
CGCGTCACCGAGCGCTGCAACTGCACCTTCCACTGGTGCTGCCACGTCAGCTGCCGCAACTGCA
CGCACACGCGCGTACTGCACGAGTGTCTGTGA

Figure 18

AGCAGAGCGGACGGGCGCGCGGGAGGCGCGCAGAGCTTTCGGGCTGCAGGCGCTCGCTGCCGC
TGGGGAATTGGGCTGTGGGCGAGGCGGTCCGGGCTGGCCTTTATCGCTCGCTGGGCCCATCGTT
TGAAACTTTATCAGCGAGTCGCCACTCGTCGCAGGACCGAGCGGGGGGCGGGGGCGCGGCGAG
GCGGCGGCCGTGACGAGGCGCTCCCGGAGCTGAGCGCTTCTGCTCTGGGCACGCATGGCGCCC
GCACACGGAGTCTGACCTGATGCAGACGCAAGGGGGTTAATATGAACGCCCCTCTCGGTGGAA
TCTGGCTCTGGCTCCCTCTGCTCTTGACCTGGCTCACCCCCGAGGTCAACTCTTCATGGTGGTAC
ATGAGAGCTACAGGTGGCTCCTCCAGGGTGATGTGCGATAATGTGCCAGGCCTGGTGAGCAGC
CAGCGGCAGCTGTGTCACCGACATCCAGATGTGATGCGTGCCATTAGCCAGGGCGTGGCCGAG
TGGACAGCAGAATGCCAGCACCAGTTCCGCCAGCACCGCTGGAATTGCAACACCCTGGACAGG
GATCACAGCCTTTTTGGCAGGGTCCTACTCCGAAGTAGTCGGGAATCTGCCTTTGTTTATGCCAT
CTCCTCAGCTGGAGTTGTATTTGCCATCACCAGGGCCTGTAGCCAAGGAGAAGTAAAATCCTGT
TCCTGTGATCCAAAGAAGATGGGAAGCGCCAAGGACAGCAAAGGCATTTTTGATTGGGGTGGC
TGCAGTGATAACATTGACTATGGGATCAAATTTGCCCGCGCATTTGTGGATGCAAAGGAAAGG
AAAGGAAAGGATGCCAGAGCCCTGATGAATCTTCACAACAACAGAGCTGGCAGGAAGGCTGTA
AAGCGGTTCTTGAAACAAGAGTGCAAGTGCCACGGGGTGAGCGGCTCATGTACTCTCAGGACA
TGCTGGCTGGCCATGGCCGACTTCAGGAAAACGGGCGATTATCTCTGGAGGAAGTACAATGGG
GCCATCCAGGTGGTCATGAACCAGGATGGCACAGGTTTCACTGTGGCTAACGAGAGGTTTAAG
AAGCCAACGAAAAATGACCTCGTGTATTTTGAGAATTCTCCAGACTACTGTATCAGGGACCGAG
AGGCAGGCTCCCTGGGTACAGCAGGCCGTGTGTGCAACCTGACTTCCCGGGGCATGGACAGCT
GTGAAGTCATGTGCTGTGGGAGAGGCTACGACACCTCCCATGTCACCCGGATGACCAAGTGTG
GGTGTAAGTTCCACTGGTGCTGCGCCGTGCGCTGTCAGGACTGCCTGGAAGCTCTGGATGTGCA
CACATGCAAGGCCCCCAAGAACGCTGACTGGACAACCGCTACATGACCCCAGCAGGCGTCACC
ATCCACCTTCCCTTCTACAAGGACTCCATTGGATCTGCAAGAACACTGGACCTTTGGGTTCTTTC
TGGGGGGATATTTCCTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTCTTCCTCCCTGGG
GGCCCCAGGATGGGGGGCCACACGCTGCACCTAAAGCCTACCCTATTCTATCCATCTCCTGGTG
TTCTGCAGTCATCTCCCCTCCTGGCGAGTTCTCTTTGGAAATAGCATGACAGGCTGTTCAGCCGG
GAGGGTGGTGGGCCCAGACCACTGTCTCCACCCACCTTGACGTTTCTTCTTTCTAGAGCAGTTG

GCCAAGCAGAAAAAAAAAGTGTCTCAAAGGAGCTTTCTCAATGTCTTCCCACAAATGGTCCCAAT
TAAGAAATTCCATACTTCTCTCAGATGGAACAGTAAAGAAAGCAGAATCAACTGCCCCTGACTT
AACTTTAACTTTTGAAAAGACCAAGACTTTTGTCTGTACAAGTGGTTTTACAGCTACCACCCTTA
GGGTAATTGGTAATTACCTGGAGAAGAATGGCTTTCAATACCCTTTTAAGTTTAAAATGTGTAT
TTTTCAAGGCATTTATTGCCATATTAAAATCTGATGTAACAAGGTGGGGACGTGTGTCCTTTGGT
ACTATGGTGTGTTGTATCTTTGTAAGAGCAAAAGCCTCAGAAAGGGATTGCTTTGCATTACTGT
CCCCTTGATATAAAAAATCTTTAGGGAATGAGAGTTCCTTCTCACTTAGAATCTGAAGGGAATT
AAAAAGAAGATGAATGGTCTGGCAATATTCTGTAACTATTGGGTGAATATGGTGGAAAATAAT
TTAGTGGATGGAATATCAGAAGTATATCTGTACAGATCAAGAAAAAAAGGAAGAATAAAATTC
CTATATCAT

Figure 19

CGGGAGTCTTCGGGGAGCTATGCTGAGACCGGGTGGTGCGGAGGAAGCTGCGCAGCTCCCGCT
TCGGCGCGCCAGCGCCCCGGTCCCTGTGCCGTCGCCCGCGGCCCCCGACGGCTCCCGGGCTTCG
GCCCGCCTAGGTCTTGCCTGCCTTCTGCTCCTGCTGCTGCTGACGCTGCCGGCCCGCGTAGACAC
GTCCTGGTGGTACATTGGGGCACTGGGGGCACGAGTGATCTGTGACAATATCCCTGGTTTGGTG
AGCCGGCAGCGGCAGCTGTGCCAGCGTTACCCAGACATCATGCGTTCAGTGGGCGAGGGTGCC
CGAGAATGGATCCGAGAGTGTCAGCACCAATTCCGCCACCACCGCTGGAACTGTACCACCCTG
GACCGGGACCACACCGTCTTTGGCCGTGTCATGCTCAGAAGTAGCCGAGAGGCAGCTTTTGTAT
ATGCCATCTCATCAGCAGGGGTAGTCCACGCTATTACTCGCGCCTGTAGCCAGGGTGAACTGAG
TGTGTGCAGCTGTGACCCCTACACCCGTGGCCGACACCATGACCAGCGTGGGGACTTTGACTGG
GGTGGCTGCAGTGACAACATCCACTACGGTGTCCGTTTTGCCAAGGCCTTCGTGGATGCCAAGG
AGAAGAGGCTTAAGGATGCCCGGGCCCTCATGAACTTACATAATAACCGCTGTGGTCGCACGG
CTGTGCGGCGGTTTCTGAAGCTGGAGTGTAAGTGCCATGGCGTGAGTGGTTCCTGTACTCTGCG
CACCTGCTGGCGTGCACTCTCAGATTTCCGCCGCACAGGTGATTACCTGCGGCGACGCTATGAT
GGGGCTGTGCAGGTGATGGCCACCCAAGATGGTGCCAACTTCACCGCAGCCCGCCAAGGCTAT
CGCCGTGCCACCCGGACTGATCTTGTCTACTTTGACAACTCTCCAGATTACTGTGTCTTGGACAA
GGCTGCAGGTTCCCTAGGCACTGCAGGCCGTGTCTGCAGCAAGACATCAAAAGGAACAGACGG
TTGTGAAATCATGTGCTGTGGCCGAGGGTACGACACAACTCGAGTCACCCGTGTTACCCAGTGT
GAGTGCAAATTCCACTGGTGCTGTGCTGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTC
CATACTTGCAAAGCCCCCAAGAAGGCAGAGTGGCTGGACCAGACCTGAACACACAGATACCTC
ACTCATCCCTCCAATTCAAGCCTCTCAACTCAAAAGCACAAGATCCTTGCATGCACACCTTCCT
CCACCCTCCACCCTGGGCTGCTACCGCTTCTATTTAAGGATGTAGAGAGTAATCCATAGGGACC
ATGGTGTCCTGGCTGGTTCCTTAGCCCTGGGAAGGAGTTGTCAGGGGATATAAGAAACTGTGCA
AGCTCCCTGATTTCCCGCTCTGGAGATTTGAAGGGAGAGTAGAAGAGATAGGGGGTCTTTAGA
GTGAAATGAGTTGCACTAAAGTACGTAGTTGAGGCTCCTTTTTTCTTTCCTTTGCACCAGCTTCC
CGACACTTCTTGGTGTGCAAGAGGAAGGGTACCTGTAGAGAGCTTCTTTTTGTTTCTACCTGGC
CAAAGTTAGATGGGACAAAGATGAATGGCATGTCCCTTCTCTGAAGTCCGTTTGAGCAGAACTA
CCTGGTACCCCGAAAGAAAAATCTTAGGCTACCACATTCTATTATTGAGAGCCTGAGATGTTAG
CCATAGTGGACAAGGTTCCATTCACATGCTCATATGTTTATAAACTGTGTTTTGTAGAAGAAAA
AGAATCATAACAATACAAACACACATTCATTCTCTCTTTTTCTCTCTACCATTCTCAACCTGTAT
TGGACAGCACTGCCTCTTTTGCTTACTTGCTGCCTGTTCAAACTGAGGTGGAATGCAGTGGTTCC
CATGCTTAACAGATCATTAAAACACCCTAGAACACTCCTAGGATAGATTAATGT

Figure 20

GCGCTTCTGACAAGCCCGAAAGTCATTTCCAATCTCAAGTGGACTTTGTTCCAACTATTGGGGG
CGTCGCTCCCCCTCYTCATGGTCGCGGGCAAACTTCCTCCTCGGCGCCTCTTCTAATGGAGCCCC
ACCTGCTCGGGCTGCTCCTCGGCCTCCTGCTCGGTGGCACCAGGGTCCTCGCTGGCTACCCAAT
TTGGTGGTCCCTGGCCCTGGGCCAGCAGTACACATCTCTGGGCTCACAGCCCCTGCTCTGCGGC
TCCATCCCAGGCCTGGTCCCCAAGCAACTGCGCTTCTGCCGCAATTACATCGAGATCATGCCCG

CGTGGCCGAGGGCGTGAAGCTGGGCATCCAGGAGTGCCAGCACCAGTTCCGGGGCCGCCGCT

GGAACTGCACCACCATAGATGACAGCCTGGCCATCTTTGGGCCCGTCCTCGACAAAGCCACCCG
CGAGTCGGCCTTCGTTCACGCCATCGCCTCGGCCGGCGTGGCCTTCGCCGTCACCCGCTCCTGC
GCCGAGGGCACCTCCACCATTTGCGGCTGTGACTCGCATCATAAGGGGCCGCCTGGCGAAGGC
TGGAAGTGGGGCGGCTGCAGCGAGGACGCTGACTTCGGCGTGTTAGTGTCCAGGGAGTTCGCG
GATGCGCGCGAGAACAGGCCGGACGCGCGCTCGGCCATGAACAAGCACAACAACGAGGCGGG
CCGCACGACTATCCTGGACCACATGCACCTCAAATGCAAGTGCCACGGGCTGTCGGGCAGCTGT
GAGGTGAAGACCTGCTGGTGGGCGCAGCCTGACTTCCGTGCCATCGGTGACTTCCTCAAGGACA
AGTATGACAGCGCCTCGGAGATGGTAGTAGAGAAGCACCGTGAGTCCCGAGGCTGGGTGGAGA
CCCTCCGGGCCAAGTACTCGCTCTTCAAGCCACCCACGGAGAGGGACCTGGTCTACTACGAGA
ACTCCCCCAACTTTTGTGAGCCCAACCCAGAGACGGGTTCCTTTGGCACAAGGGACCGGACTTG
CAATGTCACCTCCCACGGCATCGATGGCTGCGATCTGCTCTGCTGTGGCCGGGGCCACAACACG
AGGACGGAGAAGCGGAAGGAAAAATGCCACTGCATCTTCCACTGGTGCTGCTACGTCAGCTGC
CAGGAGTGTATTCGCATCTACGACGTGCACACCTGCAAGTAGGGCACCAG

Figure 21

ATGAGTCCCCGCTCGTGCCTGCGTTCGCTGCGCCTCCTCGTCTTCGCCGTCTTCTCAGCCGCCGC
GAGCAACTGGCTGTACCTGGCCAAGCTGTCGTCGGTGGGGAGCATCTCAGAGGAGGAGACGTG
CGAGAAACTCAAGGGCCTGATCCAGAGGCAGGTGCAGATGTGCAAGCGGAACCTGGAAGTCAT
GGACTCGGTGCGCCGCGGTGCCCAGCTGGCCATTGAGGAGTGCCAGTACCAGTTCCGGAACCG
GCGCTGGAACTGCTCCACACTCGACTCCTTGCCCGTCTTCGGCAAGGTGGTGACGCAAGGGATT
CGGGAGGCGGCCTTGGTGTACGCCATCTCTTCGGCAGGTGTGGCCTTTGCAGTGACGCGGGCGT
GCAGCAGTGGGGAGCTGGAGAAGTGCGGCTGTGACAGGACAGTGCATGGGGTCAGCCCACAG
GGCTTCCAGTGGTCAGGATGCTCTGACAACATCGCCTACGGTGTGGCCTTCTCACAGTCGTTTG
TGGATGTGCGGGAGAGAAGCAAGGGGGCCTCGTCCAGCAGAGCCCTCATGAACCTCCACAACA
ATGAGGCCGGCAGGAAGGCCATCCTGACACACATGCGGGTGGAATGCAAGTGCCACGGGGTGT
CAGGCTCCTGTGAGGTAAAGACGTGCTGGCGAGCCGTGCCGCCCTTCCGCCAGGTGGGTCACG
CACTGAAGGAGAAGTTTGATGGTGCCACTGAGGTGGAGCCACGCCGCGTGGGCTCCTCCAGGG
CACTGGTGCCACGCAACGCACAGTTCAAGCCGCACACAGATGAGGACTTGGTGTACTTGGAGC
CTAGCCCCGACTTCTGTGAGCAGGACATGCGCAGCGGCGTGCTGGGCACGAGGGGCCGCACAT
GCAACAAGACGTCCAAGGCCATCGACGGCTGTGAGCTGCTGTGCTGTGGCCGCGGCTTCCACA
CGGCGCAGGTGGAGCTGGCTGAACGCTGCAGCTGCAAATTCCACTGGTGCTGCTTCGTCAAGTG
CCGGCAGTGCCAGCGGCTCGTGGAGTTGCACACGTGCCGATGA

Figure 22

ATTAATTCTGGCTCCACTTGTTGCTCGGCCCAGGTTGGGGAGAGGACGGAGGGTGGCCGCAGC
GGGTTCCTGAGTGAATTACCCAGGAGGGACTGAGCACAGCACCAACTAGAGAGGGGTCAGGGG
GTGCGGGACTCGAGCGAGCAGGAAGGAGGCAGCGCCTGGCACCAGGGCTTTGACTCAACAGA
ATTGAGACACGTTTGTAATCGCTGGCGTGCCCCGCGCACAGGATCCCAGCGAAAATCAGATTTC
CTGGTGAGGTTGCGTGGGTGGATTAATTTGGAAAAAGAAACTGCCTATATCTTGCCATCAAAAA
ACTCACGGAGGAGAAGCGCAGTCAATCAACAGTAAACTTAAGAGACCCCCGATGCTCCCCTGG
TTTAACTTGTATGCTTGAAAATTATCTGAGAGGGAATAAACATCTTTTCCTTCTTCCCTCTCCAG
AAGTCCATTGGAATATTAAGCCCAGGAGTTGCTTTGGGGATGGCTGGAAGTGCAATGTCTTCCA
AGTTCTTCCTAGTGGCTTTGGCCATATTTTTCTCCTTCGCCCAGGTTGTAATTGAAGCCAATTCTT
GGTGGTCGCTAGGTATGAATAACCCTGTTCAGATGTCAGAAGTATATATTATAGGAGCACAGCC
TCTCTGCAGCCAACTGGCAGGACTTTCTCAAGGACAGAAGAAACTGTGCCACTTGTATCAGGAC
CACATGCAGTACATCGGAGAAGGCGCGAAGACAGGCATCAAAGAATGCCAGTATCAATTCCGA
CATCGACGGTGGAACTGCAGCACTGTGGATAACACCTCTGTTTTTGGCAGGGTGATGCAGATAG
GCAGCCGCGAGACGGCCTTCACATACGCCGTGAGCGCAGCAGGGGTGGTGAACGCCATGAGCC
GGGCGTGCCGCGAGGGCGAGCTGTCCACCTGCGGCTGCAGCCGCGCCGCGCGCCCCAAGGACC

TGCCGCGGGACTGGCTCTGGGGCGGCTGCGGCGACAACATCGACTATGGCTACCGCTTTGCCAA
GGAGTTCGTGGACGCCCGCGAGCGGGAGCGCATCCACGCCAAGGGCTCCTACGAGAGTGCTCG
CATCCTCATGAACCTGCACAACAACGAGGCCGGCCGCAGGACGGTGTACAACCTGGCTGATGT
GGCCTGCAAGTGCCATGGGGTGTCCGGCTCATGTAGCCTGAAGACATGCTGGCTGCAGCTGGC
AGACTTCCGCAAGGTGGGTGATGCCCTGAAGGAGAAGTACGACAGCGCGGCGGCCATGCGGCT
CAACAGCCGGGGCAAGTTGGTACAGGTCAACAGCCGCTTCAACTCGCCCACCACACAAGACCT
GGTCTACATCGACCCCAGCCCTGACTACTGCGTGCGCAATGAGAGCACCGGCTCGCTGGGCAC
GCAGGGCCGCCTGTGCAACAAGACGTCGGAGGGCATGGATGGCTGCGAGCTCATGTGCTGCGG
CCGTGGGTACGACCAGTTCAAGACCGTGCAGACGGAGCGCTGCCACTGCAAGTTCCACTGGTG
CTGCTACGTCAAGTGCAAGAAGTGCACGGAGATCGTGGACCAGTTTGTGTGCAAGTAGTGGGT
GCCACCCAGCACTCAGCCCCGCTCCCAGGACCCGCTTATTTATAGAAAGTACAGTGATTCTGGT
TTTTGGTTTTTAGAAATATTTTTTATTTTTCCCCAAGAATTGCAACCGGAACCATTTTTTTTCCTG
TTACCATCTAAGAACTCTGTGGTTTATTATTAATATTATAATTATTATTTGGCAATAATGGGGGT
GGGAACCACGAAAAATATTTATTTTGTGGATCTTTGAAAAGGTAATACAAGACTTCTTTTGGAT
AGTATAGAATGAAGGGGGAAATAACACATACCCTAACTTAGCTGTGTGGGACATGGTACACAT
CCAGAAGGTAAAGAAATACATTTTCTTTTTCTCAAATATGCCATCATATGGGATGGGTAGGTTC
CAGTTGAAAGAGGGTGGTAGAAATCTATTCACAATTCAGCTTCTATGACCAAAATGAGTTGTAA
ATTCTCTGGTGCAAGATAAAAGGTCTTGGGAAAACAAAACAAAACAAAACAAACCTCCCTTCC
CCAGCAGGGCTGCTAGCTTGCTTTCTGCATTTTCAAAATGATAATTTACAATGGAAGGACAAGA
ATGTCATATTCTCAAGGAAAAAAGGTATATCACATGTCTCATTCTCCTCAAATATTCCATTTGCA
GACAGACCGTCATATTCTAATAGCTCATGAAATTTGGGCAGCAGGGAGGAAAGTCCCCAGAAA
TTAAAAAATTTAAAACTCTTATGTCAAGATGTTGATTTGAAGCTGTTATAAGAATTGGGATTCC
AGATTTGTAAAAAGACCCCCAATGATTCTGGACACTAGATTTTTTGTTTGGGGAGGTTGGCTTG
AACATAAATGAAATATCCTGTATTTTCTTAGGGATACTTGGTTAGTAAATTATAATAGTAGAAA
TAATACATGAATCCCATTCACAGGTTTCTCAGCCCAAGCAACAAGGTAATTGCGTGCCATTCAG
CACTGCACCAGAGCAGACAACCTATTTGAGGAAAAACAGTGAAATCCACCTTCCTCTTCACACT
GAGCCCTCTCTGATTCCTCCGTGTTGTGATGTGATGCTGGCCACGTTTCCAAACGGCAGCTCCAC
TGGGTCCCCTTTGGTTGTAGGACAGGAAATGAAACATTAGGAGCTCTGCTTGGAAAACAGTTCA
CTACTTAGGGATTTTTGTTTCCTAAAACTTTTATTTTGAGGAGCAGTAGTTTTCTATGTTTTAATG
ACAGAACTTGGCTAATGGAATTCACAGAGGTGTTGCAGCGTATCACTGTTATGATCCTGTGTTT
AGATTATCCACTCATGCTTCTCCTATTGTACTGCAGGTGTACCTTAAAACTGTTCCCAGTGTACT
TGAACAGTTGCATTTATAAGGGGGGAAATGTGGTTTAATGGTGCCTGATATCTCAAAGTCTTTT
GTACATAACATATATATATATATATACATATATATAAATATAAATATAAATATATCTCATTGCAGC
CAGTGATTTAGATTTACAGCTTACTCTGGGGTTATCTCTCTGTCTAGAGCATTGTTGTCCTTCAC
TGCAGTCCAGTTGGGATTATTCCAAAAGTTTTTTGAGTCTTGAGCTTGGGCTGTGGCCCCGCTGT
GATCATACCCTGAGCACGACGAAGCAACCTCGTTTCTGAGGAAGAAGCTTGAGTTCTGACTCAC
TGAAATGCGTGTTGGGTTGAAGATATCTTTTTTTCTTTTCTGCCTCACCCCTTTGTCTCCAACCTC
CATTTCTGTTCACTTTGTGGAGAGGGCATTACTTGTTCGTTATAGACATGGACGTTAAGAGATAT
TCAAAACTCAGAAGCATCAGCAATGTTTCTCTTTTCTTAGTTCATTCTGCAGAATGGAAACCCAT
GCCTATTAGAAATGACAGTACTTATTAATTGAGTCCCTAAGGAATATTCAGCCCACTACATAGA
TAGCTTTTTTTTTTTTTTTTTTTTTTTAATAAGGACACCTCTTTCCAAACAGGCCATCAAATATGT
TCTTATCTCAGACTTACGTTGTTTTAAAAGTTTGGAAAGATACACATCTTTTCATACCCCCCCTT
AGGAGGTTGGGCTTTCATATCACCTCAGCCAACTGTGGCTCTTAATTTATTGCATAATGATATCC
ACATCAGCCAACTGTGGCTCTTTAATTTATTGCATAATGATATTCACATCCCCTCAGTTGCAGTG
AATTGTGAGCAAAAGATCTTGAAAGCAAAAAGCACTAATTAGTTTAAAATGTCACTTTTTTTGGT
TTTTATTATACAAAAACCATGAAGTACTTTTTTTATTTGCTAAATCAGATTGTTCCTTTTTAGTGA
CTCATGTTTATGAAGAGAGTTGAGTTTAACAATCCTAGCTTTTAAAAGAAACTATTTAATGTAA
AATATTCTACATGTCATTCAGATATTATGTATATCTTCTAGCCTTTATTCTGTACTTTTAATGTAC
ATATTTCTGTCTTGCGTGATTTGTATATTTCACTGGTTTAAAAAACAAACATCGAAAGGCTTATT
CCAAATGGAAG

Figure 23

GGCACGAGCGCAGGAGACACAGGCGCTGGCTGCCCCGTCCGCTCTCCGCCTCCGCCGCGCCCTCCTCGCC
CGGG ATGGGCCCCCCCGCCGCCGCCGGATCCCTCGCCTCCCGGCCGCCGCCGTTGCGCTCGCCGCGCTCG
CACTGAAGCCCGGGCCCTCGCGCGCCGCGGTTCGCCCCGCAGCCTCGCCCCCTGCCCACCCGGGCGGCCG

TAGGGCGGTCACG ATGCTGCCGCCCTTACCCTCCCGCCTCGGGCTGCTGCTGCTGCTGCTCCTGTGCCCG
GCGCACGTCGGCGGACTGTGGTGGGCTGTGGGCAGCCCCTTGGTTATGGACCCTACCAGCATCTGCAGGA
AGGCACGGCGGCTGGCCGGGCGGCAGGCCGAGTTGTGCCAGGCTGAGCCGGAAGTGGTGGCAGAGCTAGC
TCGGGGCGCCCGGCTCGGGGTGCGAGAGTGCCAGTTCCAGTTCCGCTTCCGCCGCTGGAATTGCTCCAGC
CACAGCAAGGCCTTTGGACGCATCCTGCAACAGGACATTCGGGAGACGGCCTTCGTGTTCGCCATCACTG
CGGCCGGCGCCAGCCACGCCGTCACGCAGGCCTGTTCTATGGGCGAGCTGCTGCAGTGCGGCTGCCAGGC
GCCCCGCGGGCGGGCCCCTCCCCGGCCCTCCGGCCTGCCCGGCACCCCCGGACCCCCTGGCCCCGCGGGC
TCCCCGGAAGGCAGCGCCGCCTGGGAGTGGGGAGGCTGCGGCGACGACGTGGACTTCGGGGACGAGAAGT
CGAGGCTCTTTATGGACGCGCGGCACAAGCGGGGACGCGGAGACATCCGCGCGTTGGTGCAACTGCACAA
CAACGAGGCGGGCAGGCTGGCCGTGCGGAGCCACACGCGCACCGAGTGCAAATGCCACGGGCTGTCGGGA
TCATGCGCGCTGCGCACCTGCTGGCAGAAGCTGCCTCCATTTCGCGAGGTGGGCGCGCGGCTGCTGGAGC
GCTTCCACGGCGCCTCACGCGTCATGGGCACCAACGACGGCAAGGCCCTGCTGCCCGCCGTCCGCACGCT
CAAGCCGCCGGGCCGAGCGGACCTCCTCTACGCCGCCGATTCGCCCGACTTTTGCGCCCCCAACCGACGC
ACCGGCTCCCCCGGCACGCGCGGTCGCGCCTGCAATAGCAGCGCCCCGGACCTCAGCGGCTGCGACCTGC
TGTGCTGCGGCCGCGGGCACCGCCAGGAGAGCGTGCAGCTCGAAGAGAACTGCCTGTGCCGCTTCCACTG
GTGCTGCGTAGTACAGTGCCACCGTTGCCGTGTGCGCAAGGAGCTCAGCCTCTGCCTGTGACCCGCCGCC
CGGCCGCTAGACTGACTTCGCGCAGCGGTGGCTCGCACCTGTGGGACCTCAGGGCACCGGCACCGGGCGC
CTCTCGCCGCTCGAGCCCAGCCTCTCCCTGCCAAAGCCCAACTCCCAGGGCTCTGGAAATGGTGAGGCGA
GGGGCTTGAGAGGAACGCCCACCCACGAAGGCCCAGGGCGCCAGACGGCCCCGAAAAGGCGCTCGGGGAG
CGTTTAAAGGACACTGTACAGGCCCTCCCTCCCCTTGGCCTCTAGGAGGAAACAGTTTTTAGACTGGAA
AAAAGCCAGTCTAAAGGCCTCTGGATACTGGGCTCCCCAGAACTGCTGGCCACAGGATGGTGGGTGAGGT
TAGTATCAATAAAGATATTTAAACCAAAAAAAAAAAAAAAAAAAA

Figure 24

CACGCGTCCGGGCCAATCGGGACTATGAACCGGAAAGCGCTGCGCTGCCTGGGCCACCTCTTTC
TCAGCCTGGGCATGGTCTGCCTCCGGATCGGTGGCTTCTCCTCAGTGGTAGCTCTGGGCGCAAC
GATCATCTGTAACAAGATCCCAGGCCTGGCTCCCAGACAGCGGGCGATCTGCCAGAGCCGGCC
CGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCTGGACGAGTGTCAGTTTCAGTTC
CGCAATGGCCGCTGGAACTGCTCTGCACTGGGAGAGCGCACCGTCTTCGGGAAGGAGCTCAAA
GTGGGGAGCCGGGACGGTGCGTTCACCTACGCCATCATTGCCGCCGGCGTGGCCCACGCCATC
ACAGCTGCCTGTACCCATGGCAACCTGAGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAG
TACCACCGGGACGAGGGCTGGAAGTGGGGTGGCTGCTCTGCCGACATCCGCTACGGCATCGGC
TTCGCCAAGGTCTTTGTGGATGCCCGGGAGATCAAGCAGAATGCCCGGACTCTCATGAACTTGC
ACAACAACGAGGCAGGCCGAAAGATCCTGGAGGAGAACATGAAGCTGGAATGTAAGTGCCAC
GGCGTGTCAGGCTCGTGCACCACCAAGACGTGCTGGACCACACTGCCACAGTTTCGGGAGCTG
GGCTACGTGCTCAAGGACAAGTACAACGAGGCCGTTCACGTGGAGCCTGTGCGTGCCAGCCGC
AACAAGCGGCCCACCTTCCTGAAGATCAAGAAGCCACTGTCGTACCGCAAGCCCATGGACACG
GACCTGGTGTACATCGAGAAGTCGCCCAACTACTGCGAGGAGGACCCGGTGACCGGCAGTGTG
GGCACCCAGGGCCGCGCCTGCAACAAGACGGCTCCCCAGGCCAGCGGCTGTGACCTCATGTGC
TGTGGGCGTGGCTACAACACCCACCAGTACGCCCGCGTGTGGCAGTGCAACTGTAAGTTCCACT
GGTGCTGCTATGTCAAGTGCAACACGTGCAGCGAGCGCACGGAGATGTACACGTGCAAGTGAG
CCCCGTGTGCACACCACCCTCCCGCTGCAAGTCAGATTGCTGGGAGGACTGGACCGTTTCCAAG
CTGCGGGCTCCCTGGCAGGATGCTGAGCTTGTCTTTTCTGCTGAGGAAGGTACTTTTCCTGGGTT
TCCTGCAGGCATCCGTGGGGGAAAAAAAATCTCTCAGAACCCTCAACTATTCTGTTCCACACCC
AATGCTGCTCCACCCTCCCCCAGACACAGCCCAAGTCCCTCCGCGGCTGGAGCGAAGCCTTCTG
CAGCAGGAACTCTGGACCCCTGGGCCTCATCACAGCAATATTTAACAATTTATTCTGATAAAAA
TAATATTAATTTATTTAATTAAAAAGAATTCTTCCACCTCAAAAAAAAAAAAAAAAAAAAAAAA
AAAAGGGGGG

Figure 25

TCCGCTTACACACCAAGGAAAGTTGGGCTTTGAAGAATTCCATCCCCATGGCCACTGGAGGAA
GAATATTTCNCCCGTCTTGCTTACCCATCTCCCCAGTTTTTGGAATTTTCTCTAGCTGTTACTCC
AGAGGATTATGTTTCTTTCAAAGCCTTCTGTGTACATCTGTCTTTTCACCTGTGTCCTCCAACTC
AGCCACAGCTGGTCGGTGAACAATTTCCTGATGACTGGTCCAAAGGCTTACCTGATTTACTCCA
GCAGTGTGGCAGCTGGTGCCCAGAGTGGTATTGAAGAATGCAAGTATCAGTTTGCCTGGGACC
GCTGGAACTGCCCTGAGAGAGCCCTGCAGCTGTCCAGCCATGGTGGGCTTCGCAGTGCCAATCG
GGAGACAGCATTTGTGCATGCCATCAGTTCTGCTGGAGTCATGTACACCCTGACTAGAAACTGC
AGCCTTGGAGATTTTGATAACTGTGGCTGTGATGACTCCCGCAACGGGCAACTGGGGGGACAA
GGCTGGCTGTGGGGAGGCTGCAGTGACAATGTGGGCTTCGGAGAGGCGATTTCCAAGCAGTTT
GTCGATGCCCTGGAAACAGGACAGGATGCACGGGCAGCCATGAACCTGCACAACAACGAGGCT
GGCCGCAAGGCGGTGAAGGGCACCATGAAACGCACGTGTAAGTGCCATGGCGTGTCTGGCAGC
TGCACCACGCAGACCTGTTGGCTGCAGCTGCCCGAGTTCCGCGAGGTGGGCGCGCACCTGAAG
GAGAAGTACCACGCAGCACTCAAGGTGGACCTGCTGCAGGGTGCTGGCAACAGCGCGGCCGCC
CGCGGCGCCATCGCCGACACCTTTCGCTCCATCTCTACCCGGGAGCTGGTGCACCTGGAGGACT
CCCCGGACTACTGCCTGGAGAACAAAACGCTAGGGCTGCTGGGCACCGAAGGCCGAGAGTGCC
TAAGGCGCGGGCGGGCCCTGGGTCGCTGGGAACTCCGCAGCTGCCGCCGGCTCTGCGGGGACT
GCGGGCTGGCGGTGGAGGAGCGCCGGGCCGAGACCGTGTCCAGCTGCAACTGCAAGTTCCACT
GGTGCTGTGCAGTCCGCTGCGAGCAGTGCCGCCGGAGGGTCACCAAGTACTTCTGTAGCCGCGC
AGAGCGGCCGCGGGGGGGCGCTGCGCACAAACCCGGGAGAAAACCCTAAGGGTTTCCTCTGCC
CCCTCCTTTTCCCACTGGTTCTTGGCTTCCTTTAGAGACCCCGGTAATTGTGGAACCTAGGGAAT
GGGGAACCCGCTCTCCCAGACCTAGGGATCCTGAAAGGGAAAAACTGCAATTTCTCCAAAGCT
TGCCACTTTCCAGCCTGTTTCCCCAATTCCTCTGTGCTCTCCTAAAGCTCTGTCTGAATCCTCGC
AGCCACACCTAGGTCTGAAAACTCAGGCTTTGAGTTACTGATCTTCCTTGGATTAGGAAAACAG
GTGTTCCTCCTCCCCTCTCCTATCAGCCCTAATCTCTGACCTAGCCTATCAACCCTTAGGCGCTG
GAAAAACCTTCTCATACACGCAGGACCCAGGTTAACTCAAAGCTTTGCCCTTTTGCCCACTGTC
TGCTACCAGGGGCTCACCCTCTGCTGCACCTCTCTTCTGCACAGCTCCTCCCCTGCTACTGCTGA
CCAAATTCCCAGGAATCTTGAATGCTTTCTCTCCTCTTCTCCCTTTCCTTTCCCAAAAAAAACTG
AGGAAACTGGCCCCGGAAAAGCATGTCTTTGGGGTTGGTTCCTAGAGGCAGAGGTTGAAGATG
GAAGAGGGAGCTCTGGAGTGCTAACTTGAACACCAAGGGTGCTACTCATCCCTATGGTATCATA
TCATGAATGGACTTTACTAGTGGGGCAATGACTTTCCTAGACAATAACCCGAGGGACTCCAGAT
ACATACCCCGAAGGTCTAGGAAATACGTTAAGGGCAGATTACAGTCATTTCCTACCCTTTAAAG
GTAACTTCTCCCTTCTCCTGACCTACTTCCTCCTAGCAACCAACTTTACCTCTTCTTCTCCAAAGG
ATCTTTGTTCCTCTGAGCCAAGACTGAGGTAAATAAAGCCACTTTCCTCTTCAGATCCTGGTCTG
CACCTCTAGA

Figure 26

GCGGCCGCGTCGACGGAGGGGCTGCAGCTCCGTCAGCCCGGCAGAGCCACCCTGAGCTCGGTG
AGAGCAAAGCCAGAGCCCCCAGTCCTTTGCTCGCCGGCTTGCTATCTCTCTCGATCACTCCCTCC
CTTCCTCCCTCCCTTCCTCCCGGCGGCCGCGGCGGCGCTGGGGAAGCGGTGAAGAGGAGTGGCC
CGGCCCTGGAAGAATGCGGCTCTGACAAGGGGACAGAACCCAGCGCAGTCTCCCCACGGTTTA
AGCAGCACTAGTGAAGCCCAGGCAACCCAACCGTGCCTGTCTCGGACCCCGCACCCAAACCAC
TGGAGGTCCTGATCGATCTGCCCACCGGAGCCTCCGGGCTTCGACATGCTGGAGGAGCCCCGGC
CGCGGCCTCCGCCCTCGGGCCTCGCGGGTCTCCTGTTCCTGGCGTTGTGCAGTCGGGCTCTAAG
CAATGAGATTCTGGGCCTGAAGTTGCCTGGCGAGCCGCCGCTGACGGCCAACACCGTGTGCTTG
ACGCTGTCCGGCCTGAGCAAGCGGCAGCTAGACCTGTGCCTGCGCAACCCCGACGTGACGGCG
TCCGCGCTTCAGGGTCTGCACATCGCGGTCCACGAGTGTCAGCACCAGCTGCGCGACCAGCGCT
GGAACTGCTCCGCGCTTGAGGGCGGCGGCCGCCTGCCGCACCACAGCGCCATCCTCAAGCGCG
GTTTCCGAGAAAGTGCTTTTTCCTTCTCCATGCTGGCTGCTGGGGTCATGCACGCAGTAGCCAC
GGCCTGCAGCCTGGGCAAGCTGGTGAGCTGTGGCTGTGGCTGGAAGGGCAGTGGTGAGCAGGA
TCGGCTGAGGGCCAAACTGCTGCAGCTGCAGGCACTGTCCCGAGGCAAGAGTTTCCCCCACTCT
CTGCCCAGCCCTGGCCCTGGCTCAAGCCCCAGCCCTGGCCCCCAGGACACATGGGAATGGGGT
GGCTGTAACCATGACATGGACTTTGGAGAGAAGTTCTCTCGGGATTTCTTGGATTCCAGGGAAG
CTCCCCGGGACATCCAGGCACGAATGCGAATCCACAACAACAGGGTGGGGCGCCAGGTGGTAA
CTGAAAACCTGAAGCGGAAATGCAAGTGTCATGGCACATCAGGCAGCTGCCAGTTCAAGACAT

GCTGGAGGGCGGCCCCAGAGTTCCGGGCAGTGGGGGCGGCGTTGAGGGAGCGGCTGGGCCGG
GCCATCTTCATTGATACCCACAACCGCAATTCTGGAGCCTTCCAGCCCCGTCTGCGTCCCCGTCG
CCTCTCAGGAGAGCTGGTCTACTTTGAGAAGTCTCCTGACTTCTGTGAGCGAGACCCCACTATG
GGCTCCCCAGGGACAAGGGGCCGGGCCTGCAACAAGACCAGCCGCCTGTTGGATGGCTGTGGC
AGCCTGTGCTGTGGCCGTGGGCACAACGTGCTCCGGCAGACACGAGTTGAGCGCTGCCATTGCC
GCTTCCACTGGTGCTGCTATGTGCTGTGTGATGAGTGCAAGGTTACAGAGTGGGTGAATGTGTG
TAAGTGAGGGTCAGCCTTACCTTGGGGCTGGGGAAGAGGACTGTGTGAGAGGGGCGCCTTTTC
AGCCCTTTGCTCTGATTTCCTTCCAAGGTCACTCTTGGTCCCTGGAAGCTTAAAGTATCTACCTG
GAAACAGCTTTAGGGGTGGTGGGGGTCAGGTGGACTCTGGGATGTGTAGCCTTCTCCCCAACA
ATTGGAGGGTCTTGAGGGGAAGCTGCCACCCCTCTTCTGCTCCTTAGACACCTGAATGGACTAA
GATGAAATGCACTGTATTGCTCCTCCCACTTCTCAACTCCAGAGCCCCTTTAACCCTGATTCATA
CTCCTTTTGGCTGGGGAGTCCCTATAGTTTCACCACTCCTCTCCCTTGAGGGATAACCCCAGGCA
CTGTTTGGAGCCATAAGATCTGTATCTAGAAAGAGATCACCCACTCCTATGTACTATCCCCAAA
CTCCTTTACTGCAGCCTGGGCTCCCTCTTGTGGGATAATGGGAGACAGTGGTAGAGAGGTTTTT
CTTGGGAAAGAGACAGAGTGCTGAGGGGCACTCTCCCCTGAATCCTCAGAGAGTTGTCTGTCCA
GGCCCTTAGGGAAGTTGTCTCCTTCCATTCAGATGTTAATGGGGACCCTCCAAAGGAAGGGGTT
TTCCCATGACTCTTGGAGCCTCTTTTTCCTTCTTCAGCAGGAAGGGTGGAAGGGATAATTTATC
ATACTGAGACTTGTTCTTGGTTCCTGTTTGAAACTAAAATAAATTAAGTTACTGGAAAAAAAAA
AAAAAAAAA

Figure 27

TAACCCGCCGCCTCCGCTCTCCCCGGCTGCAGGCGGCGTGCAGGACCAGCGGCGGCCGTGCAG
GCGGAGGACTTCGGCGCGGCTCCTCCTGGGTGTGACCCCGGGCGCGCCCGCCGCGCGACGATG
AGGGCGCGGCCGCAGGTCTGCGAGGCGCTGCTCTTCGCCCTGGCGCTCCAGACCGGCGTGTGCT
ATGGCATCAAGTGGCTGGCGCTGTCCAAGACACCATCGGCCCTGGCACTGAACCAGACGCAAC
ACTGCAAGCAGCTGGAGGGTCTGGTGTCTGCACAGGTGCAGCTGTGCCGCAGCAACCTGGAGC
TCATGCACACGGTGGTGCACGCCGCCCGCGAGGTCATGAAGGCCTGTCGCCGGGCCTTTGCCGA
CATGCGCTGGAACTGCTCCTCCATTGAGCTCGCCCCCAACTATTTGCTTGACCTGGAGAGAGGG
ACCCGGGAGTCGGCCTTCGTGTATGCGCTGTCGGCCGCCACCATCAGCCACGCCATCGCCCGGG
CCTGCACCTCCGGCGACCTGCCCGGCTGCTCCTGCGGCCCCGTCCCAGGTGAGCCACCCGGGCC
CGGGAACCGCTGGGGAAGATGTGCGGACAACCTCAGCTACGGGCTCCTCATGGGGGCCAAGTT
TTCCGATGCTCCTATGAAGGTGAAAAAAACAGGATCCCAAGCCAATAAACTGATGCGTCTACA
CAACAGTGAAGTGGGGAGACAGGCTCTGCGCGCCTCTCTGGAAATGAAGTGTAAGTGCCATGG
GGTGTCTGGCTCCTGCTCCATCCGCACCTGCTGGAAGGGGCTGCAGGAGCTGCAGGATGTGGCT
GCTGACCTCAAGACCCGATACCTGTCGGCCACCAAGGTAGTGCACCGACCCATGGGCACCCGC
AAGCACCTGGTGCCCAAGGACCTGGATATCCGGCCTGTGAAGGACTGGGAACTTGTTTATTTGC
AGAGCTCACCTGACTTTTGCATGAAGAATGAGAAGGTGGGCTCCCACGGGACACAAGACAGGC
AGTGCAACAAGACTTCCAACGGAAGCGACAGCTGCGACCTTATGTGCTGCGGGCGTGGCTACA
ACCCCTACACAGACCGCGTGGTCGAGCGGTGCCACTGTAAGTACCACTGGTGTTGCTACGTCAC
CTGCCGCAGGTGTGAGCGTACCGTGGAGCGCTATGTCTGCAAGTGAGGCCCTGCCCTCCGCCCC
ACGCAGGAGCGAGGACTTTGCTCAAGGACCCTCAGCAACTGGGGCCGGGGGCCTGGAGACACT
CCATGGAGCTCTGCTTGTGAATTCCAGATGCCAGGCATGGGAGGCGGCTTGTGCTTTGCCTTCA
CTTGGAAGCCACCAGGAACAGAAGGTCTGGCCACCCTGGAAGGAGNGCAGGACATCAAAGGA
AACCGACAAGATTAAAAATAACTTGGCAGCCTGAGNTCTGGAGTGCCCACAGNNTGGTGTAAG
GAGCGGGGCTTGGGATCGGTGAGACTGATACAGACTTGACCTTTCAGGGCCACAGAGACCAGC
CTCCGGGAAGGGGTCTGCCCGCCTTCTTCAGAATGTTCTGCGGGACCCCCCTGGCCCACCCTGGG
GTCTGAGCCTGCTGGGCCACCACATGGAATCACTAGCTTCGGGTTGTAAATGTTTTCTTTTGTTT
NTTGCTTTTTCTTCCTTTGGGATGTTGGAAGCTACAGAAATATTTATAAAACATAGCTTTTTCTT
TGGGGTGGCACTTCTCAATTCCTCTTTATATATTTTANATATATAAATATATATGTATATATATA
ATGATCTCTAATNTAAAACTAGCTTTTTAAGCAGCTGTATGAAATAAATGCTGAGTGAGCCCCA
GCCCGCCCCTGCAGTTCCCGGCCTCGTCAAGTGAACTCGGCAGACCCTGGGGCTGGCAGAGGG
AGCTCTCCAGTTTCCGGGCA

Figure 28

GGCGCGGCAAGATGCTGGATGGGTCCCCGCTGGCGCGCTGGCTGGCCGCGGCCTTCGGGCTGA
CGCTGCTGCTCGCCGCGCTGCGCCCTTCGGCCGCCTACTTCGGGCTGACGGGCAGCGAGCCCCT
GACCATCCTCCCGCTGACCCTGGAGCCAGAGGCGGCCGCCCAGGCGCACTACAAGGCCTGCGA
CCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCCGCCGGGACCCGGGCGTGGCAGAGA
CGCTGGTGGAGGCCGTGAGCATGAGTGCGCTCGAGTGCCAGTTCCAGTTCCGCTTTGAGCGCTG
GAACTGCACGCTGGAGGGCCGCTACCGGGCCAGCCTGCTCAAGCGAGGCTTCAAGGAGACTGC
CTTCCTCTATGCCATCTCCTCGGCTGGCCTGACGCACGCACTGGCCAAGGCGTGCAGCGCGGGC
CGCATGGAGCGCTGTACCTGCGATGAGGCACCCGACCTGGAGAACCGTGAGGCCTGGCAGTGG
GGGGGCTGCGGAGACAACCTTAAGTACAGCAGCAAGTTCGTCAAGGAATTCCTGGGCAGACGG
TCAAGCAAGGATCTGCGAGCCCGTGTGGACTTCCACAACAACCTCGTGGGTGTGAAGGTGATC
AAGGCTGGGGTGGAGACCACCTGCAAGTGCCACGGCGTGTCAGGCTCATGCACGGTGCGGACC
TGCTGGCGGCAGTTGGCGCCTTTCCATGAGGTGGGCAAGCATCTGAAGCACAAGTATGAGACG
GCACTCAAGGTGGGCAGCACCACCAATGAAGCTGCCGGCGAGGCAGGTGCCATCTCCCCACCA
CGGGGCCGTGCCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCCGCACTCCAGAGCTGGTGCAC
CTGGATGACTCGCCTAGCTTCTGCCTGGCTGGCCGCTTCTCCCCGGGCACCGCTGGCCGTAGGT
GCCACCGTGAGAAGAACTGCGAGAGCATCTGCTGTGGCCGCGGCCATAACACACAGAGCCGGG
TGGTGACAAGGCCCTGCCAGTGCCAGGTGCGTTGGTGCTGCTATGTGGAGTGCAGGCAGTGCA
CGCAGCGTGAGGAGGTCTACACCTGCAAGGGCTGAGTTCCCAGGCCCTGCCAGCCCTGCTGCA
CAGGGTGCAGGCATTGCACACGGTGTGAAGGGTCTACACCTGCACAGGCTGAGTTCCTGGGCT
CGACCAGCCCAGCTGCGTGGGGTACAGGCATTGCACACAGTGTGAATGGGTCTACACCTGCAT
GGGCTGAGTCCCTGGGCTCAGACCTAGCAGCGTGGGGTAGTCCCTGGGCTCAGTCCTAGCTGCA
TGGGGTGCAGGCATTGCACAGAGCATGAATGGGCCTACACCTGCCAAGGCTGAATCCCTGGGC
CCAGCCAGCCCTGCTGCACATGGCACAGGCATTGCACACGGTGTGAGGAGTGTACACCTGCAA
GGGCTGAGGCCCTGGGCCCAGTCAGCCCTGCTGCTCAGAGTGCAGGCATTGCACATGGTGTGA
GAAGGTCTACACCTGCAAGGGACGAGTCCCCGGGCCTGGCCAACCCTGCTGTGCAGGGTGAGG
GCCATGCATGCTAGTATGAGGGGTCTACACCTGCAAGGACTGAGAGGCTTTT

Figure 29

AGCCTGCAAAAACCACAGAGGGCAAAGCCAGAAAGATGGAAAGGCACCCACCCATGCAGCTC
ACCACTTGCCTCAGGGAGACCCTCTTCACAGGGGCTTCTCAAAAGACCTCCCTATGGTGGTTGG
GCATTGCCTCCTTCGGGGTTCCAGAGAAGCTGGGCTGCGCCAATTTGCCGCTGAACAGCCGCCA
GAAGGAGCTGTGCAAGAGGAAACCGTACCTGCTGCCGAGCATCCGAGAGGGCGCCCGGCTGGG
CATTCAGGAGTGCAGGAGCCAGTTCAGACACGAGAGATGGAACTGCATGATCACCGCCGCCGC
CACTACCGCCCCGATGGGCGCCAGCCCCCTCTTTGGCTACGAGCTGAGCAGCGGCACCAAAGA
GACAGCATTTATTTATGCTGTGATGGCTGCAGGCCTGGTGCATTCTGTGACCAGGTCATGCAGT
GCAGGCAACATGACAGAGTGTTCCTGTGACACCACCTTGCAGAACGGCGGCTCAGCAAGTGAA
GGCTGGCACTGGGGGGGCTGCTCCGATGATGTCCAGTATGGCATGTGGTTCAGCAGAAAGTTCC
TAGATTTCCCCATCGGAAACACCACGGGCAAAGAAAACAAAGTACTATTAGCAATGAACCTAC
ATAACAATGAAGCTGGAAGGCAGGCTGTCGCCAAGTTGATGTCAGTAGACTGCCGCTGCCACG
GAGTTTCCGGCTCCTGTGCTGTGAAAACATGCTGGAAAACCATGTCTTCTTTTGAAAAGATTGG
CCATTTGTTGAAGGATAAATATGAAAACAGTATCCAGATATCAGACAAAATAAAGAGGAAAAT
GCGCAGGAGAGAAAAAGATCAGAGGAAAATACCAATCCATAAGGATGATCTGCTCTATGTTAA
TAAGTCTCCCAACTACTGTGTAGAAGATAAGAAACTGGGAATCCCAGGGACACAAGGCAGAGA
ATGCAACCGTACATCAGAGGGTGCAGATGGCTGCAACCTCCTCTGCTGTGGCCGAGGTTACAAC
ACCCATGTGGTCAGGCACGTGGAGAGGTGTGAGTGTAAGTTCATCTGGTGCTGCTATGTCCGTT
GCAGGAGGTGTGAAAGCATGACTGATGTCCACACTTGCAAGTAACCACTCCATCCAGCCTTGG
GCAAGATGCCTCAGCAATATACAATGGCATTGCAACCAGAGAGGTGCCCATCCCTGTGCAGCG
CTAGTAAAGTTGACTCTTGCAGTGGAATCCC

Figure 30

AGTTGAGGGATTGACACAAATGGTCAGGCGGCGGCGGCGGAGAAGGAGGCGGAGGCGCAGGG
GGGAGCCGAGCCCGCTGGGCTGCGGAGAGTTGCGCTCTCTACGGGGCCGCGGCCACTAGCGCG
GCGCCGCCAGCCGGGAGCCAGCGAGCCGAGGGCCAGGAAGGCGGGACACGACCCCGGCGCGC
CCTAGCCACCCGGGTTCTCCCCGCCGCCCGCGCTTCATGAATCGCAAGTTTCCGCGGCGGCGGC
GGCTGCGGTACGCAGAACAGGAGCCGGGGGAGCGGGCCGAAAGCGGCTTGGGCTCGACGGAG
GGCACCCGCGCAGAGGTCTCCCTGGCCGCAGGGGGAGCCGCCGCCGGCCGTGCCCCTGGCAGC
CCCAGCGGAGCGGCGCCAAGAGAGGAGCCGAGAAAGTATGGCTGAGGAGGAGGCGCCTAAGA
AGTCCCGGGCCGCCGGCGGTGGCGCGAGCTGGGAACTTTGTGCCGGGGCGCTCTCGGCCCGGC
TGGCGGAGGAGGGCAGCGGGGACGCCGGTGGCCGCCGCCGCCCGCCAGTTGACCCCCGGCGAT
TGGCGCGCCAGCTGCTGCTGCTGCTTTGGCTGCTGGAGGCTCCGCTGCTGCTGGGGGTCCGGGC
CCAGGCGGCGGGCCAGGGGCCAGGCCAGGGGCCCGGGCCGGGGCAGCAACCGCCGCCGCCGC
CTCAGCAGCAACAGAGCGGGCAGCAGTACAACGGCGAGCGGGGCATCTCCGTCCCGGACCACG
GCTATTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCGTACAACCAGACCATCATGCC
CAACCTGCTGGGCCACACGAACCAGGAGGACGCGGGCCTGGAGGTGCACCAGTTCTACCCTCT
AGTGAAAGTGCAGTGTTCCGCTGAGCTCAAGTTCTTCCTGTGCTCCATGTACGCGCCCGTGTGC
ACCGTGCTAGAGCAGGCGCTGCCGCCCTGCCGCTCCCTGTGCGAGCGCGCGCGCCAGGGCTGC
GAGGCGCTCATGAACAAGTTCGGCTTCCAGTGGCCAGACACGCTCAAGTGTGAGAAGTTCCCG
GTGCACGGCGCCGGCGAGCTGTGCGTGGGCCAGAACACGTCCGACAAGGGCACCCCGACGCCC
TCGCTGCTTCCAGAGTTCTGGACCAGCAACCCTCAGCACGGCGGCGGAGGGCACCGTGGCGGC
TTCCCGGGGGGCGCCGGCGCGTCGGAGCGAGGCAAGTTCTCCTGCCCGCGCGCCCTCAAGGTG
CCCTCCTACCTCAACTACCACTTCCTGGGGGAGAAGGACTGCGGCGCACCTTGTGAGCCGACCA
AGGTGTATGGGCTCATGTACTTCGGGCCCGAGGAGCTGCGCTTCTCGCGCACCTGGATTGGCAT
TTGGTCAGTGCTGTGCTGCGCCTCCACGCTCTTCACGGTGCTTACGTACCTGGTGGACATGCGG
CGCTTCAGCTACCCGGAGCGGCCCATCATCTTCTTGTCCGGCTGTTACACGGCCGTGGCCGTGG
CCTACATCGCCGGCTTCCTCCTGGAAGACCGAGTGGTGTGTAATGACAAGTTCGCCGAGGACGG
GGCACGCACTGTGGCGCAGGGCACCAAGAAGGAGGGCTGCACCATCCTCTTCATGATGCTCTA
CTTCTTCAGCATGGCCAGCTCCATCTGGTGGGTGATCCTGTCGCTCACCTGGTTCCTGGCGGCTG
GCATGAAGTGGGGCCACGAGGCCATCGAAGCCAACTCACAGTATTTTCACCTGGCCGCCTGGG
CTGTGCCGGCCATCAAGACCATCACCATCCTGGCGCTGGGCCAGGTGGACGGCGATGTGCTGA
GCGGAGTGTGCTTCGTGGGGCTTAACAACGTGGACGCGCTGCGTGGCTTCGTGCTGGCGCCCCT
CTTCGTGTACCTGTTTATCGGCACGTCCTTTCTGCTGGCCGGCTTTGTGTCGCTCTTCCGCATCCG
CACCATCATGAAGCACGATGGCACCAAGACCGAGAAGCTGGAGAAGCTCATGGTGCGCATTGG
CGTCTTCAGCGTGCTGTACACTGTGCCAGCCACCATCGTCATCGCCTGCTACTTCTACGAGCAG
GCCTTCCGGGACCAGTGGGAACGCAGCTGGGTGGCCCAGAGCTGCAAGAGCTACGCTATCCCC
TGCCCTCACCTCCAGGCGGGCGGAGGCGCCCCGCCGCACCCGCCCATGAGCCCGGACTTCACG
GTCTTCATGATTAAGTACCTTATGACGCTGATCGTGGGCATCACGTCGGGCTTCTGGATCTGGTC
CGGCAAGACCCTCAACTCCTGGAGGAAGTTCTACACGAGGCTCACCAACAGCAAACAAGGGGA
GACTACAGTCTGAGACCCGGGGCTCAGCCCATGCCCAGGCCTCGGCCGGGGCGCAGCGATCCC
CCAAAGCCAGCGCCGTGGAGTTCGTGCCAATCCTGACATCTCGAGGTTTCCTCACTAGACAACT
CTCTTTCGCAGGCTCCTTTGAACAACTCAGCTCCTGCAAAAGCTTCCGTCCCTGAGGCAAAAGG
ACACGAGGGCCCGACTGCCAGAGGGAGGATGGACAGACCTCTTGCCCTCACACTCTGGTACCA
GGACTGTTCGCTTTTATGATTGTAAATAGCCTGTGTAAGATTTTTGTAAGTATATTTGTATTTAA
ATGACGACCGATCACGCGTTTTTCTTTTTCAAAAGTTTTTAATTATTTAGGGCGGTTTAACCATT
TGAGGCTTTTCCTTCTTGCCCTTTTCGGAGTATTGCAAAGGAGCTAAAACTGGTGTGCAACCGC
ACAGCGCTCCTGGTCGTCCTCGCGCGCCTCTCCCTACCACGGGTGCTCGGGACGGCTGGGCGCC
AGCTCCGGGGCGAGTTCAGCACTGCGGGGTGCGACTAGGGCTGCGCTGCCAGGGTCACTTCCC
GCCTCCTCCTTTTGCCCCCTCCCCCTCCTTCTGTCCCCTCCCTTTCTTTCCTGGCTTGAGGTAGGG
GCTCTTAAGGTACAGAACTCCACAAACCTTCCAAATCTGGAGGAGGGCCCCCATACATTACAAT
TCCTCCCTTGCTCGGCGGTGGATTGCGAAGGCCCGTCCCTTCGACTTCCTGAAGCTGGATTTTTA
ACTGTCCAGAACTTTCCTCCAACTTCATGGGGGCCCACGGGTGTGGGCGCTGGCAGTCTCAGCC
TCCCTCCACGGTCACCTTCAACGCCCAGACACTCCCTTCTCCCACCTTAGTTGGTTACAGGGTGA
GTGAGATAACCAATGCCAAACTTTTTGAAGTCTAATTTTTGAGGGGTGAGCTCATTTCATTCTCT
AGTGTCTAAAACCTGGTATGGGTTTGGCCAGCGTCATGGAAAGATGTGGTTACTGAGATTTGGG
AAGAAGCATGAAGCTTTGTGTGGGTTGGAAGAGACTGAAGATATGGGTTATAAAATGTTAATT
CTAATTGCATACGGATGCCTGGCAACCTTGCCTTTGAGAATGAGACAGCCTGCGCTTAGATTTT
ACCGGTCTGTAAAATGGAAATGTTGAGGTCACCTGGAAAGCTTTGTTAAGGAGTTGATGTTTGC

TTTCCTTAACAAGACAGCAAAACGTAAACAGAAATTGAAAACTTGAAGGATATTTCAGTGTCAT
GGACTTCCTCAAAATGAAGTGCTATTTTCTTATTTTTAATCAAATAACTAGACATATATCAGAA
ACTTTAAAATGTAAAAGTTGTACACTTTCAACATTTTATTACGATTATTATTCAGCAGCACATTC
TGAGGGGGGAACAATTCACACCACCAATAATAACCTGGTAAGATTTCAGGAGGTAAAGAAGGT
GGAATAATTGACGGGGAGATAGCGCCTGAAATAAACAAAATATGGGCATGCATGCTAAAGGG
AAAATGTGTGCAGGTCTACTGCATTAAATCCTGTGTGCTCCTCTTTTGGATTTACAGAAATGTGT
CAAATGTAAATCTTTCAAAGCCATTTAAAAATATTCACTTTAGTTCTCTGTGAAGAAGAGGAGA
AAAGCAATCCTCCTGATTGTATTGTTTTAAACTTTAAGAATTTATCAAAATGCCGGTACTTAGG
ACCTAAATTTATCTATGTCTGTCATACGCTAAAATGATATTGGTCTTTGAATTTGGTATACATTT
ATTCTGTTCACTATCACAAAATCATCTATATTTATAGAGGAATAGAAGTTTATATATATATAATA
CCATATTTTTAATTTCACAAATAAAAAATTCAAAGTTTTGTACAAAATTATATGGATTTTGTGCC
TGAAAATAATAGAGCTTGAGCTGTCTGAACTATTTTACATTTTATGGTGTCTCATAGCCAATCCC
ACAGTGTAAAAATTCA

Figure 31

CGAGTAAAGTTTGCAAAGAGGCGCGGAGGCGGCAGCCGCAGCGAGGAGGCGGCGGGGAAGA
AGCGCAGTCTCCGGGTTGGGGGCGGGGGCGGGGGGGGCGCCAAGGAGCCGGGTGGGGGGCGG
CGGCCAGCATGCGGCCCCGCAGCGCCCTGCCCCGCCTGCTGCTGCCGCTGCTGCTGCTGCCCCGC
CGCCGGGCCGGCCCAGTTCCACGGGGAGAAGGGCATCTCCATCCCGGACCACGGCTTCTGCCA
GCCCATCTCCATCCCGCTGTGCACGGACATCGCCTACAACCAGACCATCATGCCCAACCTTCTG
GGCCACACGAACCAGGAGGACGCAGGCCTAGAGGTGCACCAGTTCTATCCGCTGGTGAAGGTG
CAGTGCTCGCCCGAACTGCGCTTCTTCCTGTGCTCCATGTACGCACCCGTGTGCACCGTGCTGG
AACAGGCCATCCCGCCGTGCCGCTCTATCTGTGAGCGCGCGCGCCAGGGCTGCGAAGCCCTCAT
GAACAAGTTCGGTTTTCAGTGGCCCGAGCGCCTGCGCTGCGAGCACTTCCCGCGCCACGGCGCC
GAGCAGATCTGCGTCGGCCAGAACCACTCCGAGGACGGAGCTCCCGCGCTACTCACCACCGCG
CCGCCGCCGGGACTGCAGCCGGGTGCCGGGGGCACCCCGGGTGGCCCGGGCGGCGGCGGCGCT
CCCCCGCGCTACGCCACGCTGGAGCACCCCTTCCACTGCCCGCGCGTCCTCAAGGTGCCATCCT
ATCTCAGCTACAAGTTTCTGGGCGAGCGTGATTGTGCTGCGCCCTGCGAACCTGCGCGGCCCGA
TGGTTCCATGTTCTTCTCACAGGAGGAGACGCGTTTCGCGCGCCTCTGGATCCTCACCTGGTCG
GTGCTGTGCTGCGCTTCCACCTTCTTCACTGTCACCACGTACTTGGTAGACATGCAGCGCTTCCG
CTACCCAGAGCGGCCTATCATTTTTCTGTCGGGCTGCTACACCATGGTGTCGGTGGCCTACATC
GCGGGCTTCGTGCTCCAGGAGCGCGTGGTGTGCAACGAGCGCTTCTCCGAGGACGGTTACCGC
ACGGTGGTGCAGGGCACCAAGAAGGAGGGCTGCACCATCCTCTTCATGATGCTCTACTTCTTCA
GCATGGCCAGCTCCATCTGGTGGGTCATCCTGTCGCTCACCTGGTTCCTGGCAGCCGGCATGAA
GTGGGGCCACGAGGCCATCGAGGCCAACTCTCAGTACTTCCACCTGGCCGCCTGGGCCGTGCCG
GCCGTCAAGACCATCACCATCCTGGCCATGGGCCAGATCGACGGCGACCTGCTGAGCGGCGTG
TGCTTCGTAGGCCTCAACAGCCTGGACCCGCTGCGGGGCTTCGTGCTAGCGCCGCTCTTCGTGT
ACCTGTTCATCGGCACGTCCTTCCTCCTGGCCGGCTTCGTGTCGCTCTTCCGCATCCGCACCATC
ATGAAGCACGACGGCACCAAGACCGAAAAGCTGGAGCGGCTCATGGTGCGCATCGGCGTCTTC
TCCGTGCTCTACACAGTGCCCGCCACCATCGTCATCGCTTGCTACTTCTACGAGCAGGCCTTCCG
CGAGCACTGGGAGCGCTCGTGGGTGAGCCAGCACTGCAAGAGCCTGGCCATCCCGTGCCCGGC
GCACTACACGCCGCGCATGTCGCCCGACTTCACGGTCTACATGATCAAATACCTCATGACGCTC
ATCGTGGGCATCACGTCGGGCTTCTGGATCTGGTCGGGCAAGACGCTGCACTCGTGGAGGAAG
TTCTACACTCGCCTCACCAACAGCCGACACGGTGAGACCACCGTGTGAGGGACGCCCCCAGGC
CGGAACCGCGCGGCGCTTTCCTCCGCCCGGGGTGGGGCCCCTACAGACTCCGTATTTTATTTTTT
TAAATAAAAAACGATCGAAACCATTTCACTTTTAGGTTGCTTTTTAAAAGAGAACTCTCTGCCC
AACACCCCC

Figure 32

GCCGCTCCGGGTACCTGAGGGACGCGCGGCCGCCCGCGGCAGGCGGTGCAGCCCCCCCCCACC
CCTTGGAGCCAGGCGCCGGGGTCTGAGGATAGCATTTCTCAAGACCTGACTTATGGAGCACTTG
TAACCTGAGATATTTCAGTTGAAGGAAGAAATAGCTCTTCTCCTAAGATGGAATCTGTGGTTTG

GGAATGTGGTTGATCAACTTGATATGTTGGCCAAATGTGCCCCATGTAATAAAATGAAAAGAA
GAGACAAGATGATGTCATTTTCCCATATTGTGAAACCAAAAACAAACGCCTTTTGTGAGACCAA
GCTAACAAACCTCTGACGGTGCGAAGAGTATTTAACTGTTTGAAGAATTTAACAGTAAGATACA
GAAGAAGTACCTTCGAGCTGAGACCTGCAGGTGTATAAATATCTAAAATACATATTGAATAGG
CCTGATCATCTGAATCTCCTTCAGACCCAGGAAGGATGGCTATGACTTGGATTGTCTTCTCTCTT
TGGCCCTTGACTGTGTTCATGGGGCATATAGGTGGGCACAGTTTGTTTCTTGTGAACCTATTAC
CTTGAGGATGTGCCAAGATTTGCCTTATAATACTACCTTCATGCCTAATCTTCTGAATCATTATG
ACCAACAGACAGCAGCTTTGGCAATGGAGCCATTCCACCCTATGGTGAATCTGGATTGTTCTCG
GGATTTCCGGCCTTTTCTTTGTGCACTCTACGCTCCTATTTGTATGGAATATGGACGTGTCACAC
TTCCCTGTCGTAGGCTGTGTCAGCGGGCTTACAGTGAGTGTTCGAAGCTCATGGAGATGTTTGG
TGTTCCTTGGCCTGAAGATATGGAATGCAGTAGGTTCCCAGATTGTGATGAGCCATATCCTCGA
CTTGTGGATCTGAATTTAGCTGGAGAACCAACTGAAGGAGCCCCAGTGGCAGTGCAGAGAGAC
TATGGTTTTTGGTGTCCCCGAGAGTTAAAAATTGATCCTGATCTGGGTTATTCTTTTCTGCATGT
GCGTGATTGTTCACCTCCTTGTCCAAATATGTACTTCAGAAGAGAAGAACTGTCATTTGCTCGCT
ATTTCATAGGATTGATTTCAATCATTTGCCTCTCGGCCACATTGTTTACTTTTTTAACTTTTTTGA
TTGATGTCACAAGATTCCGTTATCCTGAAAGGCCTATTATATTTTATGCAGTCTGCTACATGATG
GTATCCTTAATTTTCTTCATTGGATTTTTGCTTGAAGATCGAGTAGCCTGCAATGCATCCATCCC
TGCACAATATAAGGCTTCCACAGTGACACAAGGATCTCATAATAAAGCCTGTACCATGCTTTTT
ATGATACTCTATTTTTTTACTATGGCTGGCAGTGTATGGTGGGTAATTCTTACCATCACATGGTT
TTTAGCAGCTGTGCCAAAGTGGGGTAGTGAAGCTATTGAGAAGAAAGCATTGCTGTTTCACGCC
AGTGCATGGGGCATCCCCGGAACTCTAACCATCATCCTTTTAGCGATGAATAAAATTGAAGGTG
ACAATATTAGTGGCGTGTGTTTTGTTGGCCTCTACGATGTTGATGCATTGAGATATTTTGTTCTT
GCTCCCCTCTGCCTGTATGTGGTAGTTGGGGTTTCTCTCCTCTTAGCTGGCATTATATCCCTAAA
CAGAGTTCGAATTGAGATTCCATTAGAAAAGGAGAACCAAGATAAATTAGTGAAGTTTATGAT
CCGGATCGGTGTTTTCAGCATTCTTTATCTCGTACCACTCTTGGTTGTAATTGGATGCTACTTTTA
TGAGCAAGCTTACCGGGGCATCTGGGAAACAACGTGGATACAAGAACGCTGCAGAGAATATCA
CATTCCATGTCCATATCAGGTTACTCAAATGAGTCGTCCAGACTTGATTCTCTTTCTGATGAAAT
ACCTGATGGCTCTCATAGTTGGCATTCCCTCTGTATTTTGGGTTGGAAGCAAAAAGACATGCTTT
GAATGGGCCAGTTTTTTTCATGGTCGTAGGAAAAAAGAGATAGTGAATGAGAGCCGACAGGTA
CTCCAGGAACCTGATTTTGCTCAGTCTCTCCTGAGGGATCCAAATACTCCTATCATAAGAAAGT
CAAGGGGAACTTCCACTCAAGGAACATCCACCCATGCTTCTTCAACTCAGCTGGCTATGGTGGA
TGATCAAAGAAGCAAAGCAGGAAGCATCCACAGCAAAGTGAGCAGCTACCACGGCAGCCTCC
ACAGATCACGTGATGGCAGGTACACGCCCTGCAGTTACAGAGGAATGGAGGAGAGACTACCTC
ATGGCAGCATGTCACGACTAACAGATCACTCCAGGCATAGTAGTTCTCATCGGCTCAATGAACA
GTCACGACATAGCAGCATCAGAGATCTCAGTAATAATCCCATGACTCATATCACACATGGCACC
AGCATGAATCGGGTTATTGAAGAAGATGGAACCAGTGCTTAATTTGTCTTGTCTAAGGTGGAAA
TCTTGTGCTGTTTAAAAAGCAGATTTTATTCTTTGCCTTTTGCATGACTGATAGCTGTACTCACA
GTTAACATGCTTTCAGTCAAGTACAGATTGTGTCCACTGGAAAGGTAAATGATTGCTTTTTTATA
TTGCATCAAACTTGGAACATCAAGGCATCCAAAACACTAAGAATTCTATCATCACAAAAATAAT
TCGTCTTTCTAGGTTATGAAGAGATAATTATTTGTCTGGTAAGCATTTTTATAAACCCACTCATT
TTATATTTAGAAAAATCCTAAATGTGTGGTGACTGCTTTGTAGTGAACTTTCATATACTATAAAC
TAGTTGTGAGATAACATTCTGGTAGCTCAGTTAATAAAACAATTTCAGAATTAAAGAAATTTTC
TATGCAAGGTTTACTTCTCAGATGAACAGTAGGACTTTGTAGTTTTATTTCCACTAAGTGAAAA
AAGAACTGTGTTTTTAAACTGTAGGAGAATTTAATAAATCAGCAAGGGTATTTTAGCTAATAGA
ATAAAAGTGCAACAGAAGAATTTGATTAGTCTATGAAAGGTTCTCTTAAAATTCTATCGAAATA
ATCTTCATGCAGAGATATTCAGGGTTTGGATTAGCAGTGGAATAAAGAGATGGGCATTGTTTCC
CCTATAATTGTGCTGTTTTTATAACTTTTGTAAATATTACTTTTTCTGGCTGTGTTTTTATAACTT
ATCCATATGCATGATGGAAAAATTTTAATTTGTAGCCATCTTTTCCCATGTAATAGTATTGATTC
ATAGAGAACTTAATGTTCAAAATTTGCTTTGTGGAGGCATGTAATAAGATAAACATCATACATT
ATAAGGTAACCACAATTACAAAATGGCAAAACA

Figure 33

GCTGCGCAGCGCTGGCTGCTGGCTGGCCTCGCGGAGACGCCGAACGGACGCGGCCGGCGCCGG
CTTGTGGGCTCGCCGCCTGCAGCCATGACCCTCGCAGCCTGTCCCTCGGCCTCGGCCCGGGACG
TCTAAAATCCCACACAGTCGCGCGCAGCTGCTGGAGAGCCGGCCGCTGCCCCCTCGTCGCCGCA

TCACACTCCCGTCCCGGGAGCTGGGAGCAGCGCGGGCAGCCGGCGCCCCCGTGCAAACTGGGG
GTGTCTGCCAGAGCAGCCCCAGCCGCTGCCGCTGCTACCCCCGATGCTGGCCATGGCCTGGCGG
GGCGCAGGGCCGAGCGTCCCGGGGGCGCCCGGGGGCGTCGGTCTCAGTCTGGGGTTGCTCCTG
CAGTTGCTGCTGCTCCTGGGGCCGGCGCGGGGCTTCGGGGACGAGGAAGAGCGGCGCTGCGAC
CCCATCCGCATCTCCATGTGCCAGAACCTCGGCTACAACGTGACCAAGATGCCCAACCTGGTTG
GGCACGAGCTGCAGACGGACGCCGAGCTGCAGCTGACAACTTTCACACCGCTCATCCAGTACG
GCTGCTCCAGCCAGCTGCAGTTCTTCCTTTGTTCTGTTTATGTGCCAATGTGCACAGAGAAGATC
AACATCCCCATTGGCCCATGCGGCGGCATGTGTCTTTCAGTCAAGAGACGCTGTGAACCCGTCC
TGAAGGAATTTGGATTTGCCTGGCCAGAGAGTCTGAACTGCAGCAAATTCCCACCACAGAACG
ACCACAACCACATGTGCATGGAAGGGCCAGGTGATGAAGAGGTGCCCTTACCTCACAAAACCC
CCATCCAGCCTGGGGAAGAGTGTCACTCTGTGGGAACCAATTCTGATCAGTACATCTGGGTGAA
AAGGAGCCTGAACTGTGTGCTCAAGTGTGGCTATGATGCTGGCTTATACAGCCGCTCAGCCAAG
GAGTTCACTGATATCTGGATGGCTGTGTGGGCCAGCCTGTGTTTCATCTCCACTGCCTTCACAGT
ACTGACCTTCCTGATCGATTCTTCTAGGTTTTCCTACCCTGAGCGCCCCATCATATTTCTCAGTA
TGTGCTATAATATTTATAGCATTGCTTATATTGTCAGGCTGACTGTAGGCCGGGAAAGGATATC
CTGTGATTTTGAAGAGGCAGCAGAACCTGTTCTCATCCAAGAAGGACTTAAGAACACAGGATG
TGCAATAATTTTCTTGCTGATGTACTTTTTTGGAATGGCCAGCTCCATTTGGTGGGTTATTCTGA
CACTCACTTGGTTTTTGGCAGCAGGACTCAAATGGGGTCATGAAGCCATTGAAATGCACAGCTC
TTATTTCCACATTGCAGCCTGGGCCATCCCCGCAGTGAAAACCATTGTCATCTTGATTATGAGA
CTGGTGGATGCAGATGAACTGACTGGCTTGTGCTATGTTGGAAACCAAAATCTCGATGCCCTCA
CCGGGTTCGTGGTGGCTCCCCTCTTTACTTATTTGGTCATTGGAACTTTGTTCATTGCTGCAGGT
TTGGTGGCCTTGTTCAAAATTCGGTCAAATCTTCAAAAGGATGGGACAAAGACAGACAAGTTA
GAAAGACTGATGGTCAAGATTGGGGTGTTCTCAGTACTGTACACAGTTCCTGCAACGTGTGTGA
TTGCCTGTTATTTTTATGAAATCTCCAACTGGGCACTTTTTCGGTATTCTGCAGATGATTCCAAC
ATGGCTGTTGAAATGTTGAAAACTTTTATGTCTTTGTTGGTGGGCATCACTTCAGGCATGTGGAT
TTGGTCTGCCAAAAGTCTTCACACGTGGCAGAAGTGTTCCAACAGATTGGTGAATTCTGGAAAG
GTAAAGAGAGAGAAGAGAGGAAATGGTTGGGTGAAGCCTGGAAAAGGCAGTGAGACTGTGGT
ATAAGGCTAGTCAGCCTCCATGCTTTCTTCATTTTGAAGGGGGGAATGCCAGCATTTTGGAGGA
AATTCTACTAAAAGTTTTATGCAGTGAATCTCAGTTTGAACAAACTAGCAACAATTAAGTGACC
CCCGTCAACCCACTGCCTCCCACCCCGACCCCAGCATCAAAAAACCAATGATTTTGCTGCAGAC
TTTGGAATGATCCAAAATGGAAAAGCCAGTTAGAGGCTTTCAAAGCTGTGAAAAATCAAAACG
TTGATCACTTTAGCAGGTTGCAGCTTGGAGCGTGGAGGTCCTGCCTAGATTCCAGGAAGTCCAG
GGCGATACTGTTTTCCCCTGCAGGGTGGGATTTGAGCTGTGAGTTGGTAACTAGCAGGGAGAAA
TATTAACTTTTTTAACCCTTTACCATTTTAAATACTAACTGGGTCTTTCAGATAGCAAAGCAATC
TATAAACACTGGAAACGCTGGGTTCAGAAAAGTGTTACAAGAGTTTTATAGTTTGGCTGATGTA
ACATAAACATCTTCTGTGGTGCGCTGTCTGCTGTTTAGAACTTTGTGGACTGCACTCCCAAGAA
GTGGTGTTAGAATCTTTCAGTGCCTTTGTCATAAAACAGTTATTTGAACAAACAAAAGTACTGT
ACTCACACACATAAGGTATCCAGTGGATTTTTCTTCTCTGTCTTCCTCTCTTAAATTTCAACATCT
CTCTTCTTGGCTGCTGCTGTTTTCTTCATTTTATGTTAATGACTCAAAAAAGGTATTTTTATAGAA
TTTTTGTACTGCAGCATGCTTAAAGAGGGGAAAAGGAAGGGTGATTCACTTTCTGACAATCACT
TAATTCAGAGGAAAATGAGATTTACTAAGTTGACTTACCTGACGGACCCCAGAGACCTATTGCA
TTGAGCAGTGGGGACTTAATATATTTTACTTGTGTGATTGCATCTATGCAGACGCCAGTCTGGA
AGAGCTGAAATGTTAAGTTTCTTGGCAACTTTGCATTCACACAGATTAGCTGTGTAATTTTTGTG
TGTCAATTACAATTAAAAGCACATTGTTGGACCATGACATAGTATACTCAACTGACTTTAAAAC
TATGGTCAACTTCAACTTGCATTCTCAGAATGATAGTGCCTTTAAAATTTTTTTATTTTTTAAAG
CATAAGAATGTTATCAGAATCTGGTCTACTTAGGACAATGGAGACTTTTTCAGTTTTATAAAGG
GAACTGAGGACAGCTAATCCAACTACTTGGTGCTGTAATTGTTTCCTAGTAATTGGCAAAGGCT
CCTTGTAAGATTTCACTGGAGGCAGTGTGGCCTGGAGTATTTATATGGTGCTTAATGAATCTCC
AGAATGCCAGCCAGAAGCCTGATTGGTTAGTAGGGAATAAAGTGTAGACCATATGAAATGAAC
TGCAAACTCTAATAGCCCAGGTCTTAATTGCCTTTAGCAGAGGTATCCAAAGCTTTTAAAATTT
ATGCATACGTTCTTCACAAGGGGGTACCCCCAGCAGCCTCTCGAAAATTGCACTTCTCTTAAAA
CTGTAACTGGCCTTTCTCTTACCTTGCCTTAGGCCTTCTAATCATGAGATCTTGGGGACAAATTG
ACTATGTCACAGGTTGCTCTCCTTGTAACTCATACCTGTCTGCTTCAGCAACTGCTTTGCAATGA
CATTTATTTATTAATTCATGCCTTAAAAAAATAGGAAGGGAAGCTTTTTTTTTTCTTTTTTTTTTT
TTCAATCACACTTTGTGGAAAAACATTTCCAGGGACTCAAAATTCCAAAAAGGTGGTCAAATTC
TGGAAGTAAGCATTTCCTCTTTTTTAAAAATTTGGTTTGAGCCTTATGCCCATAGTTTGACATTT

CCCTTTCTTCTTTCCTTTTTGTTTTTGTGTGGTTCTTGAGCTCTCTGACATCAAGATGCATGTAAA
GTCGATTGTATGTTTTGAAGGCAAAGTCTTGGCTTTTGAGACTGAAGTTAAGTGGGCACAGGTG
GCCCCTGCTGCTGTGCCCAGTCTGAGTACCTTGGCTAGACTCTAGGTCAGGCTCCAGGAGCATG
AGAATTGATCCCCAGAAGAACCATTTTAACTCCATCTGATACTCCATTGCCTATGAAATGTAAA
ATGTGAACTCCCTGTGCTGCTTGTAGACAGTTCCCATAACTGTCCACGGCCCTGGAGCACGCAC
CCAGGGGCAGAGCCTGCCCTTACTCACGCTCTGCTCTGGTGTCTTGGGAGTTGTGCAGGGACTC
TGGCCCAGGCAGGGGAAGGAAGACCAGGCGGTAGGGGACTGGTCTTGCTGTTAGAGTATAGAG
GTTTGTAATGCAGTTTTCTTCATAATGTGTCAGTGATTGTGTGACCAAGGCAGCATCTAGCAGA
AAGCCAGGCATGGAGTAGGTGATCGATACTTGTCAATGACTAAATAATAACAATAAAAGAGCA
CTTGGGTGAATCTGGGCACCTGATTTCTGAGTTTTGAGTTCTGGAGCTAGTGTTTTGACAATGCT
TTGGGTTTTGACATGCCTTTTCCACAAATCTCTTGCCTTTTCAGGGCAAAGTGTATTTGATCAGA
AGTGGCCATTTGGATTAGTAGCCTTAGCAATGCTACAGGGTTATAGGCCCCTCTCCCTTTCACAT
TCCAGACAATGGAGAGTGTTTATGGTTTCAGGAAAAGAACTTTGTGGCTGAGGGGTCAGTTACC
AGTGACCTTCAATCAACTCCATCACTTCTTAAATCGGTATTTGTTAAAAAAATCAGTTATTTTAT
TTATTGAGTGCCGACTGTAGTAAAGCCCTGAAATAGATAATCTCTGTTCTTCTAACTGATCTAG
GATGGGGACGCACCCAGGTCTGCTGAACTTTACTGTTCCTCTGGGAAAGGAGCAGGGACCTCTG
GAATTCCCATCTGTTTCACTGTCTCCATTCCATAAATCTCTTCCTGTGTGAGCCACCACACCCAG
CCTGGGTCTCTCTACTTTTAACACATCTCTCATCCCTTTCCCAGGACTTCCTTCCAAGTCAGTTAC
AGGTGGTTTTAACAGAAAGCATCAGCTCTGCTTCGTGACAGTCTCTGGAGAAATCCCTTAGGAA
GACTATGAGAGTAGGCCACAAGGACATGGCCCACACATCTGCTTTGGCTTTGCCGGCAATTCA
GGGCTTGGGGTATTCCATGTGACTTGTATAGGTATATTTGAGGACAGCATCTTGCTAGAGAAAA
GGTGAGGGTTGTTTTTCTTTCTCTGAAACCTACAGTAAATGGGTATGATTGTAGCTTCCTCAGAA
ATCCCTTGGCCTCCAGAGATTAAACATGGTGCAATGGCACCTCTGTCCAACCTCCTTTCTGGTA
GATTCCTTTCTCCTGCTTCATATAGGCCAAACCTCAGGGCAAGGGAACATGGGGGTAGAGTGGT
GCTGGCCAGAACCATCTGCTTGAGCTACTTGGTTGATTCATATCCTCTTTCCTTTATGGAGACCC
ATTTCCTGATCTCTGAGACTGTTGCTGAACTGGCAACTTACTTGGGCCTGAAACTGGAGAAGGG
GTGACATTTTTTTAATTTCAGAGATGCTTTCTGATTTTCCTCTCCCAGGTCACTGTCTCACCTGCA
CTCTCCAAACTCAGGTTCCGGGAAGCTTGTGTGTCTAGATACTGAATTGAGATTCTGTTCAGCA
CCTTTTAGCTCTATACTCTCTGGCTCCCCTCATCCTCATGGTCACTGAATTAAATGCTTATTGTAT
TGAGAACCAAGATGGGACCTGAGGACACAAAGATGAGCTCAACAGTCTCAGCCCTAGAGGAAT
AGACTCAGGGATTTCACCAGGTCGGTGCAGTATTTGATTTCTGGTGAGGTGACCACAGCTGCAG
TTAGGAAGGGAGCCATTGAGCACAGACTTTGGAAGGAACCTTTTTTTTGTTGTTTGTTTGTTTGT
TTGTTTGTTTGTTTGTTTGAGACAGGGTCTTGCTCTGCTACCCAGGCTGGGGCGCAATGGCACGA
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AGTGCTGGGATTACAAGTGTGAGCCACCACACCTGGCCTGGAAGGAACCTCTTAAAATCAGTTT
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GAGTCACTGGACTCTGAAAATCCTATTGGTTCCTTTATTTTATTTGAGTTTAGAGTTCCCTTCTG
GGTTTGTATTATGTCTGGCAAATGACCTGGGTTATCACTTTTCCTCCAGGGTTAGATCATAGATC
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GATTTCATTTCACTCTAGCCTACATAGAGCTTTCTGTTGCTGTCTCTTGCCATGCACTTGTGCGG
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CTCTTTGTAAGAAAGGTAGATGAAATATCGGATGTAATCTGAAAAAAAGATAAAATGTGACTT
CCCCTGCTCTGTGCAGCAGTCGGGCTGGATGCTCTGTGGCNTTTCTTGGGTCCTCATGCCACCCC
ACAGCTCCAGGAACCTTGAAGCCAATCTGGGGACTTTCAGATGTTTGACAAAGAGGTACCAGG
CAAACTTCCTGCTACACATGCCCTGAATGAATTGCTAAATTTCAAAGGAAATGGACCCTGCTTT
TAAGGATGTACAAAAGTATGTCTGCATCGATGTCTGTACTGTAAATTTCTAATTTATCACTGTAC

AAAGAAAACCCCTTGCTATTTAATTTTGTATTAAAGGAAAATAAAGTTTTGTTTGTTAAAAAAA
AA

Figure 34

ACCCAGGGACGGAGGACCCAGGCTGGCTTGGGGACTGTCTGCTCTTCTCGGCGGGAGCCGTGG
AGAGTCCTTTCCCTGGAATCCGAGCCCTAACCGTCTCTCCCCAGCCCTATCCGGCGAGGAGCGG
AGCGCTGCCAGCGGAGGCAGCGCCTTCCCGAAGCAGTTTATCTTTGGACGGTTTTCTTTAAAGG
AAAAACGAACCAACAGGTTGCCAGCCCCGGCGCCACACACGAGACGCCGGAGGGAGAAGCCC
CGGCCCGGATTCCTCTGCCTGTGTGCGTCCCTCGCGGGCTGCTGGAGGCGAGGGGAGGGAGGG
GGCGATGGCTCGGCCTGACCCATCCGCGCCGCCCTCGCTGTTGCTGCTGCTCCTGGCGCAGCTG
GTGGGCCGGGCGGCCGCCGCGTCCAAGGCCCCGGTGTGCCAGGAAATCACGGTGCCCATGTGC
CGCGGCATCGGCTACAACCTGACGCACATGCCCAACCAGTTCAACCACGACACGCAGGACGAG
GCGGGCCTGGAGGTGCACCAGTTCTGGCCGCTGGTGGAGATCCAATGCTCGCCGGACCTGCGCT
TCTTCCTATGCACTATGTACACGCCCATCTGTCTGCCCGACTACCACAAGCCGCTGCCGCCCTGC
CGCTCGGTGTGCGAGCGCGCCAAGGCCGGCTGCTCGCCGCTGATGCGCCAGTACGGCTTCGCCT
GGCCCGAGCGCATGAGCTGCGACCGCCTCCCGGTGCTGGGCCGCGACGCCGAGGTCCTCTGCA
TGGATTACAACCGCAGCGAGGCCACCACGGCGCCCCCCAGGCCTTTCCCAGCCAAGCCCACCCT
TCCAGGCCCGCCAGGGGCGCCGGCCTCGGGGGGCGAATGCCCCGCTGGGGGCCCGTTCGTGTG
CAAGTGTCGCGAGCCCTTCGTGCCCATTCTGAAGGAGTCACACCCGCTCTACAACAAGGTGCGG
ACGGGCCAGGTGCCCAACTGCGCGGTACCCTGCTACCAGCCGTCCTTCAGTGCCGACGAGCGC
ACGTTCGCCACCTTCTGGATAGGCCTGTGGTCGGTGCTGTGCTTCATCTCCACGTCCACCACAGT
GGCCACCTTCCTCATCGACATGGACACGTTCCGCTATCCTGAGCGCCCCATCATCTTCCTGTCAG
CCTGCTACCTGTGCGTGTCGCTGGGCTTCCTGGTGCGTCTGGTCGTGGGCCATGCCAGCGTGGC
CTGCAGCCGCGAGCACAACCACATCCACTACGAGACCACGGGCCCTGCACTGTGCACCATCGT
CTTCCTCCTGGTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTCATCCTGTCGCTCACCT
GGTTCCTGGCCGCCGCGATGAAGTGGGGCAACGAGGCCATCGCGGGCTACGGCCAGTACTTCC
ACCTGGCTGCGTGGCTCATCCCCAGCGTCAAGTCCATCACGGCACTGGCGCTGAGCTCCGTGGA
CGGGGACCCAGTGGCCGGCATCTGCTACGTGGGCAACCAGAACCTGAACTCGCTGCGGCGCTT
CGTGCTGGGCCCGCTGGTGCTCTACCTGCTGGTGGGCACGCTCTTCCTGCTGGCGGGCTTCGTGT
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CCACGACACCGGCCAGCCGCGCGCCAAGCCCGAGTACTGGGTGCTCATGCTCAAGTACTTCATG
TGCCTGGTGGTGGGCATCACGTCGGGCGTCTGGATCTGGTCGGGCAAGACGGTGGAGTCGTGG
CGGCGTTTCACCAGCCGCTGCTGCTGCCGCCCGCGGCGCGGCCACAAGAGCGGGGGCGCCATG
GCCGCAGGGGACTACCCCGAGGCGAGCGCCGCGCTCACAGGCAGGACCGGGCCGCCGGGCCCC
GCCGCCACCTACCACAAGCAGGTGTCCCTGTCGCACGTGTAGGAGGCTGCCGCCGAGGGACTC
GGCCGGAGAGCTGAGGGGAGGGGGGCGTTTTGTTTGGTAGTTTTGCCAAGGTCACTTCCGTTTA
CCTTCATGGTGCTGTTGCCCCCTCCCGCGGCGACTTGGAGAGAGGGAAGAGGGGCGTTTTCGAG
GAAGAACCTGTCCCAGGTCTTCTCCAAGGGGCCCAGCTCACGTGTATTCTATTTTGCGTTTCTTA
CCTGCCTTCTTTATGGGAACCCTCTTTTTAATTTATATGTAT

Figure 35

GCAGCTCCAGTCCCGGACGCAACCCCGGAGCCGTCTCAGGTCCCTGGGGGGAACGGTGGGTTA
GACGGGGACGGGAAGGGACAGCGGCCTTCGACCGCCCCCCGAGTAATTGACCCAGGACTCATT
TTCAGGAAAGCCTGAAAATGAGTAAAATAGTGAAATGAGGAATTTGAACATTTTATCTTTGGAT
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CTCTTCACCTGTGAACCAATTACTGTTCCCAGATGTATGAAAATGGCCTACAACATGACGTTTTT
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CTCGCAAATCTGGAATGTTCACCAAACATTGAAACTTTCCTCTGCAAAGCATTTGTACCAACCT
GCATAGAACAAATTCATGTGGTTCCACCTTGTCGTAAACTTTGTGAGAAAGTATATTCTGATTG

CAAAAAATTAATTGACACTTTTGGGATCCGATGGCCTGAGGAGCTTGAATGTGACAGATTACAA
TACTGTGATGAGACTGTTCCTGTAACTTTTGATCCACACACAGAATTTCTTGGTCCTCAGAAGA
AAACAGAACAAGTCCAAAGAGACATTGGATTTTGGTGTCCAAGGCATCTTAAGACTTCTGGGG
GACAAGGATATAAGTTTCTGGGAATTGACCAGTGTGCGCCTCCATGCCCCAACATGTATTTTAA
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CAAAATAAGGCTTGCACCGTTTTGTTCATGCTTTTGTATTTTTTCACAATGGCTGGCACTGTGTG
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CAGAATTGGCTTTATTTATGATAAAATACCTGATGACATTAATTGTTGGCATCTCTGCTGTCTTC
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GAGAGGTGAAAGCGGACGGAGCTAGCACCCCCAGGTTAAGAGAACAGGACTGTGGTGAACCT
GCCTCGCCAGCAGCATCCATCTCCAGACTCTCTGGGGAACAGGTCGACGGGAAGGGCCAGGCA
GGCAGTGTATCTGAAAGTGCGCGGAGTGAAGGAAGGATTAGTCCAAAGAGTGATATTACTGAC
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GGTTCCACATCTCTGCTTGTTCACCCAGTTTCAGGAGTGAGAAAAGAGCAGGGAGGTGGTTGTC
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AGGGTTAGTAGACAAAATGTTAGTCTTTTGTATATTAGGCCAAGTGCAATTGACTTCCCTTTTTT
AATGTTTCATGACCACCCATTGATTGTATTATAACCACTTACAGTTGCTTATATTTTTTGTTTTAA
CTTTTGTTTCTTAACATTTAGAATATTACATTTTGTATTATACAGTACCTTTCTCAGACATTTTGT
AG

Figure 36

CTCTCCCAACCGCCTCGTCGCACTCCTCAGGCTGAGAGCACCGCTGCACTCGCGGCCGGCGATG
CGGGACCCCGGCGCGGCCGCTCCGCTTTCGTCCCTGGGCCTCTGTGCCCTGGTGCTGGCGCTGC
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CGGACCACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCCTACAACCAGAC
CATCCTGCCCAACCTGCTGGGCCACACGAACCAAGAGGACGCGGGCCTCGAGGTGCACCAGTT
CTACCCGCTGGTGAAGGTGCAGTGTTCTCCCGAACTCCGCTTTTTCTTATGCTCCATGTATGCGC
CCGTGTGCACCGTGCTCGATCAGGCCATCCCGCCGTGTCGTTCTCTGTGCGAGCGCGCCCGCCA

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GGCGGCCGGCATGAAGTGGGGCCACGAGGCCATCGAGGCCAACTCGCAGTACTTCCACCTGGC
CGCGTGGGCCGTGCCCGCCGTCAAGACCATCACTATCCTGGCCATGGGCCAGGTAGACGGGGA
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GTATATTTTGTAAATCTCCCATTTTTGTAAGAAAATATATATTGTATTTATACATTTTTACTTTGG
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TTTTTAAATAC

Figure 37

ACAGCATGGAGTGGGGTTACCTGTTGGAAGTGACCTCGCTGCTGGCCGCCTTGGCGCTGCTGCA
GCGCTCTAGCGGCGCTGCGGCCGCCTCGGCCAAGGAGCTGGCATGCCAAGAGATCACCGTGCC
GCTGTGTAAGGGCATCGGCTACAACTACACCTACATGCCCAATCAGTTCAACCACGACACGCA
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GGCTTCGCCTGGCCCGACCGCATGCGCTGCGACCGGCTGCCCGAGCAAGGCAACCCTGACACG
CTGTGCATGGACTACAACCGCACCGACCTAACCACCGCCGCGCCCAGCCCGCCGCGCCGCCTGC
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CGCGGCGGCGGCGGTGGCGGGAAGGCGCGGCCCCCTGGCGGCGGCGCGGCTCCCTGCGAGCCC
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TGGCCGCGTGGCTTGTGCCCAGCGTCAAGTCCATCGCGGTGCTGGCGCTCAGCTCGGTGGACGG
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GCTGGCGCCGCTGGTCATCTACCTCTTCATCGGCACCATGTTCCTGCTGGCCGGCTTCGTGTCCC
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AGCTGATGATCCGCCTGGGCCTGTTCACCGTGCTCTACACCGTGCCCGCCGCGGTGGTGGTCGC
CTGCCTCTTCTACGAGCAGCACAACCGCCCGCGCTGGGAGGCCACGCACAACTGCCCGTGCCTG
CGGGACCTGCAGCCCGACCAGGCACGCAGGCCCGACTACGCCGTCTTCATGCTCAAGTACTTCA
TGTGCCTAGTGGTGGGCATCACCTCGGGCGTGTGGGTCTGGTCCGGCAAGACGCTGGAGTCCTG
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GCGGGGGGCCGGGCGGCGGCGGGGGCTCCCTCTACAGCGACGTCAGCACTGGCCTGACGTGGC
GGTCGGGCACGGCGAGCTCCGTGTCTTATCCAAAGCAGATGCCATTGTCCCAGGTCTGAGCGGA
GGGGAGGGGGCGCCCAGGAGGGGTGGGGAGGGGGGCGAGGAGACCCAAGTGCAGCGAAGGG
ACACTTGATGGGCTGAGGTTCCCACCCCTTCACAGTGTTGATTGCTATTAGCATGATAATGAAC
TCTTAATGGTATCCATTAGCTGGGACTTAAATGACTCACTTAGAACAAAGTACCTGGCATTGAA
GCCTCCCAGACCCAGCCCCTTTTCCTCCATTGATGTGCGGGGAGCTCCTCCCGCCACGCGTTAAT
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TATTTGTTAAATTGTAAAAAAAAAAAGTGTAAAATATGTATATATCCAAAGATATAGTGTGTAC
ATTTTTTTGTAAAAAGTTTAGAGGCTTACCCCTGTAAGAACAGATATAAGTATTCTATTTTGTCA
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ATCATTGTTGAACTGAAATCAAAATTGAGTTTTTGCACCTTCCCCAAAGACGGTGTTTTTCATGG
GAGCTCTTTTCTGATCCATGGATAACAACTCTCACTTTAGTGGATGTAAATGGAACTTCTGCAA
GGCAGTAATTCCCCTTAGGCCTTGTTATTTATCCTGCATGGTATCACTAAAGGTTTCAAAACCCT
GAAAAAAAA

Figure 38

CCGCCTTCGGCCCGGGCCTCCCGGGATGGCCGTGGCGCCTCTGCGGGGGGCGCTGCTGCTGTGG
CAGCTGCTGGCGGCGGGCGGCGCGGCACTGGAGATCGGCCGCTTCGACCCGGAGCGCGGGCGC
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CCATGTGCACCGACCAGGTCTCGACGCCCATTCCCGCCTGCCGGCCCATGTGCGAGCAGGCGCG
CCTGCGCTGCGCGCCCATCATGGAGCAGTTCAACTTCGGCTGGCCGGACTCGCTCGACTGCGCC
CGGCTGCCCACGCGCAACGACCCGCACGCGCTGTGCATGGAGGCGCCCGAGAACGCCACGGCC
GGCCCCGCGGAGCCCCACAAGGGCCTGGGCATGCTGCCCGTGGCGCCGCGGCCCGCGCGCCCT
CCCGGAGACCTGGGCCCGGGCGCGGGCGGCAGTGGCACCTGCGAGAACCCCGAGAAGTTCCAG
TACGTGGAGAAGAGCCGCTCGTGCGCACCGCGCTGCGGGCCCGGCGTCGAGGTGTTCTGGTCC
CGGCGCGACAAGGACTTCGCGCTGGTCTGGATGGCCGTGTGGTCGGCGCTGTGCTTCTTCTCCA
CCGCCTTCACTGTGCTCACCTTCTTGCTGGAGCCCCACCGCTTCCAGTACCCCGAGCGCCCCATC
ATCTTCCTCTCCATGTGCTACAACGTCTACTCGCTGGCCTTCCTGATCCGTGCGGTGGCCGGAGC
GCAGAGCGTGGCCTGTGACCAGGAGGCGGGCGCGCTCTACGTGATCCAGGAGGGCCTGGAGAA
CACGGGCTGCACGCTGGTCTTCCTACTGCTCTACTACTTCGGCATGGCCAGCTCGCTCTGGTGG
GTGGTCCTGACGCTCACCTGGTTCCTGGCTGCCGGGAAGAAATGGGGCCACGAGGCCATCGAG
GCCCACGGCAGCTATTTCCACATGGCTGCCTGGGGCCTGCCCGCGCTCAAGACCATCGTCATCC
TGACCCTGCGCAAGGTGGCGGGTGATGAGCTGACTGGGCTTTGCTACGTGGCCAGCACGGATG
CAGCAGCGCTCACGGGCTTCGTGCTGGTGCCCCTCTCTGGCTACCTGGTGCTGGGCAGTAGTTT
CCTCCTGACCGGCTTCGTGGCCCTCTTCCACATCCGCAAGATCATGAAGACGGGCGGCACCAAC
ACAGAGAAGCTGGAGAAGCTCATGGTCAAGATCGGGGTCTTCTCCATCCTCTACACGGTGCCCG
CCACCTGCGTCATCGTTTGCTATGTCTACGAACGCCTCAACATGGACTTCTGGCGCCTTCGGGCC
ACAGAGCAGCCATGCGCAGCGGCCGCGGGGCCCGGAGGCCGGAGGGACTGCTCGCTGCCAGG
GGGCTCGGTGCCCACCGTGGCGGTCTTCATGCTCAAAATTTTCATGTCACTGGTGGTGGGGATC
ACCAGCGGCGTCTGGGTGTGGAGCTCCAAGACTTTCCAGACCTGGCAGAGCCTGTGCTACCGCA
AGATAGCAGCTGGCCGGGCCCGGGCCAAGGCCTGCCGCGCCCCCGGGAGCTACGGACGTGGCA
CGCACTGCCACTATAAGGCTCCCACCGTGGTCTTGCACATGACTAAGACGGACCCCTCTTTGGA
GAACCCCACACACCTCTAGCCACACAGGCCTGGCGCGGGGTGGCTGCTGCCCCCTCCTTGCCCT
CCACGCCCTGCCCCCTGCATCCCCTAGAGACAGCTGACTAGCAGCTGCCCAGCTGTCAAGGTCA
GGCAAGTGAGCACCGGGGACTGAGGATCAGGGCGGGACCCCGTGAGGCTCATTAGGGGAGAT
GGGGGTCTCCCCTAATGCGGGGGCTGGACCAGGCTGAGTCCCCACAGGGTCCTAGTGGAGGAT
GTGGAGGGGCGGGGCAGAGGGGTCCAGCCGGAGTTTATTTAATGATGTAATTTATTGTTGCGTT
CCTCTGGAAGCTGTGACTGGAATAAACCCCCGCGTGGCACTGCTGATCCTCTCTGGCTGGGAAG
GGGGAAGGTAGGAGGTGAGGC

Figure 39

ACACGTCCAACGCCAGCATGCAGCGCCCGGGCCCCCGCCTGTGGCTGGTCCTGCAGGTGATGG
GCTCGTGCGCCGCCATCAGCTCCATGGACATGGAGCGCCCGGGCGACGGCAAATGCCAGCCCA
TCGAGATCCCGATGTGCAAGGACATCGGCTACAACATGACTCGTATGCCCAACCTGATGGGCC
ACGAGAACCAGCGCGAGGCAGCCATCCAGTTGCACGAGTTCGCGCCGCTGGTGGAGTACGGCT
GCCACGGCCACCTCCGCTTCTTCCTGTGCTCGCTGTACGCGCCGATGTGCACCGAGCAGGTCTC
TACCCCCATCCCCGCCTGCCGGGTCATGTGCGAGCAGGCCCGGCTCAAGTGCTCCCCGATTATG
GAGCAGTTCAACTTCAAGTGGCCCGACTCCCTGGACTGCCGGAAACTCCCCAACAAGAACGAC
CCCAACTACCTGTGCATGGAGGCGCCCAACAACGGCTCGGACGAGCCCACCCGGGGCTCGGGC
CTGTTCCCGCCGCTGTTCCGGCCGCAGCGGCCCCACAGCGCGCAGGAGCACCCGCTGAAGGAC
GGGGGCCCCGGGCGCGGCGGCTGCGACAACCCGGGCAAGTTCCACCACGTGGAGAAGAGCGC
GTCGTGCGCGCCGCTCTGCACGCCCGGCGTGGACGTGTACTGGAGCCGCGAGGACAAGCGCTT
CGCAGTGGTCTGGCTGGCCATCTGGGCGGTGCTGTGCTTCTTCTCCAGCGCCTTCACCGTGCTCA
CCTTCCTCATCGACCCGGCCCGCTTCCGCTACCCCGAGCGCCCCATCATCTTCCTCTCCATGTGC
TACTGCGTCTACTCCGTGGGCTACCTCATCCGCCTCTTCGCCGGCGCCGAGAGCATCGCCTGCG
ACCGGGACAGCGGCCAGCTCTATGTCATCCAGGAGGGACTGGAGAGCACCGGCTGCACGCTGG
TCTTCCTGGTCCTCTACTACTTCGGCATGGCCAGCTCGCTGTGGTGGGTGGTCCTCACGCTCACC

TGGTTCCTGGCCGCCGGCAAGAAGTGGGGCCACGAGGCCATCGAAGCCAACAGCAGCTACTTC
CACCTGGCAGCCTGGGCCATCCCGGCGGTGAAGACCATCCTGATCCTGGTCATGCGCAGGGTG
GCGGGGGACGAGCTCACCGGGGTCTGCTACGTGGGCAGCATGGACGTCAACGCGCTCACCGGC
TTCGTGCTCATTCCCCTGGCCTGCTACCTGGTCATCGGCACGTCCTTCATCCTCTCGGGCTTCGT
GGCCCTGTTCCACATCCGGAGGGTGATGAAGACGGGCGGCGAGAACACGGACAAGCTGGAGA
AGCTCATGGTGCGTATCGGGCTCTTCTCTGTGCTGTACACCGTGCCGGCCACCTGTGTGATCGCC
TGCTACTTTTACGAACGCCTCAACATGGATTACTGGAAGATCCTGGCGGCGCAGCACAAGTGCA
AAATGAACAACCAGACTAAAACGCTGGACTGCCTGATGGCCGCCTCCATCCCCGCCGTGGAGA
TCTTCATGGTGAAGATCTTTATGCTGCTGGTGGTGGGGATCACCAGCGGGATGTGGATTTGGAC
CTCCAAGACTCTGCAGTCCTGGCAGCAGGTGTGCAGCCGTAGGTTAAAGAAGAAGAGCCGGAG
AAAACCGGCCAGCGTGATCACCAGCGGTGGGATTTACAAAAAAGCCCAGCATCCCCAGAAAAC
TCACCACGGGAAATATGAGATCCCTGCCCAGTCGCCCACCTGCGTGTGAACAGGGCTGGAGGG
AAGGGCACAGGGGCGCCCGGAGCTAAGATGTGGTGCTTTTCTTGGTTGTGTTTTTCTTTCTTCTT
CTTCTTTTTTTTTTTTTTATAAAAGCAAAAGAGAAATACATAAAAAAGTGTTTACCCTGAAATTC
AGGATGCTGTGATACACTGAAAGGAAAAATGTACTTAAAGGGTTTTGTTTTGTTTTGGTTTTCC
AGCGAAGGGAAGCTCCTCCAGTGAAGTAGCCTCTTGTGTAACTAATTTGTGGTAAAGTAGTTGA
TTCAGCCCTCAGAAGAAAACTTTTGTTTAGAGCCCTCCGTAAATATACATCTGTGTATTTGAGTT
GGCTTTGCTACCCATTTACAAATAAGAGGACAGATAACTGCTTTGCAAATTCAAGAGCCTCCCC
TGGGTTAACAAATGAGCCATCCCCAGGGCCCACCCCCAGGAAGGCCACAGTGCTGGGCGGCAT
CCCTGCAGAGGAAAGACAGGACCCGGGGCCCGCCTCACACCCCAGTGGATTTGGAGTTGCTTA
AAATAGACTCTGGCCTTCACCAATAGTCTCTCTGCAAGACAGAAACCTCCATCAAACCTCACAT
TTGTGAACTCAAACGATGTGCAATACATTTTTTTCTCTTTCCTTGAAAATAAAAAGAGAAACAA
GTATTTTGCTATATATAAAGACAACAAAAGAAATCTCCTAACAAAAGAACTAAGAGGCCCAGC
CCTCAGAAACCCTTCAGTGCTACATTTTGTGGCTTTTTAATGGAAACCAAGCCAATGTTATAGA
CGTTTGGACTGATTTGTGGAAAGGAGGGGGGAAGAGGGAGAAGGATCATTCAAAAGTTACCCA
AAGGGCTTATTGACTCTTTCTATTGTTAAACAAATGATTTCCACAAACAGATCAGGAAGCACTA
GGTTGGCAGAGACACTTTGTCTAGTGTATTCTCTTCACAGTGCCAGGAAAGAGTGGTTTCTGCG
TGTGTATATTTGTAATATATGATATTTTTCATGCTCCACTATTTATTAAAAATAAAATATGTTCT
TTAAAAAAA

Figure 40

CCTGCAGCCTCCGGAGTCAGTGCCGCGCGCCCGCCGCCCCGCGCCTTCCTGCTCGCCGCACCTC
CGGGAGCCGGGGCGCACCCAGCCCGCAGCGCCGCCTCGCCGCCCGCGCCGCCTCCGACCGCAG
GCCGAGGGCCGCCACTGGCCGGGGGGACCGGGCAGCAGCTTGCGGCCGCGGAGCCGGGCAAC
GCTGGGGACTGCGCCTTTTGTCCCCGGAGGTCCCTGGAAGTTTGCGGCAGGACGCGCGCGGGG
AGGCGGCGGAGGCAGCCCCGACGTCGCGGAGAACAGGGCGCAGAGCCGGCATGGGCATCGGG
CGCAGCGAGGGGGGCCGCCGCGGGGCCCTGGGCGTGCTGCTGGCGCTGGGCGCGGCGCTTCTG
GCCGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCTTCCAGTCGGACATCGGCCCGTACCAG
AGCGGGCGCTTCTACACCAAGCCACCTCAGTGCGTGGACATCCCCGCGGACCTGCGGCTGTGCC
ACAACGTGGGCTACAAGAAGATGGTGCTGCCCAACCTGCTGGAGCACGAGACCATGGCGGAGG
TGAAGCAGCAGGCCAGCAGCTGGGTGCCCCTGCTCAACAAGAACTGCCACGCCGGGACCCAGG
TCTTCCTCTGCTCGCTCTTCGCGCCCGTCTGCCTGGACCGGCCCATCTACCCGTGTCGCTGGCTC
TGCGAGGCCGTGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGCCCGAGA
TGCTTAAGTGTGACAAGTTCCCGGAGGGGGACGTCTGCATCGCCATGACGCCGCCCAATGCCAC
CGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCCTCCCTGTGACAACGAGTTGAAATCTGA
GGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGCACTGAGGATGAAAATAAAAGAAGTGAA
AAAAGAAAATGGCGACAAGAAGATTGTCCCCAAGAAGAAGAAGCCCCTGAAGTTGGGGCCCA
TCAAGAAGAAGGACCTGAAGAAGCTTGTGCTGTACCTGAAGAATGGGGCTGACTGTCCCTGCC
ACCAGCTGGACAACCTCAGCCACCACTTCCTCATCATGGGCCGCAAGGTGAAGAGCCAGTACTT
GCTGACGGCCATCCACAAGTGGGACAAGAAAAACAAGGAGTTCAAAAACTTCATGAAGAAAA
TGAAAAACCATGAGTGCCCCACCTTTCAGTCCGTGTTTAAGTGATTCTCCCGGGGGCAGGGTGG
GGAGGGAGCCTCGGGTGGGGTGGGAGCGGGGGGGACAGTGCCCGGGAACCCGTGGTCACACA
CACGCACTGCCCTGTCAGTAGTGGACATTGTAATCCAGTCGGCTTGTTCTTGCAGCATTCCC

CCCTTTCCCTCCATAGCCACGCTCCAAACCCCAGGGTAGCCATGGCCGGGTAAAGCAAGGGCC
ATTTAGATTAGGAAGGTTTTTAAGATCCGCAATGTGGAGCAGCAGCCACTGCACAGGAGGAGG
TGACAAACCATTTCCAACAGCAACACAGCCACTAAAACACAAAAAGGGGGATTGGGCGGAAA
GTGAGAGCCAGCAGCAAAAACTACATTTTGCAACTTGTTGGTGTGGATCTATTGGCTGATCTAT
GCCTTTCAACTAGAAAATTCTAATGATTGGCAAGTCACGTTGTTTTCAGGTCCAGAGTAGTTTCT
TTCTGTCTGCTTTAAATGGAAACAGACTCATACCACACTTACAATTAAGGTCAAGCCCAGAAAG
TGATAAGTGCAGGGAGGAAAAGTGCAAGTCCATTATCTAATAGTGACAGCAAAGGGACCAGGG
GAGAGGCATTGCCTTCTCTGCCCACAGTCTTTCCGTGTGATTGTCTTTGAATCTGAATCAGCCAG
TCTCAGATGCCCCAAAGTTTCGGTTCCTATGAGCCCGGGGCATGATCTGATCCCCAAGACATGT
GGAGGGGCAGCCTGTGCCTGCCTTTGTGTCAGAAAAAGGAAACCACAGTGAGCCTGAGAGAGA
CGGCGATTTTCGGGCTGAGAAGGCAGTAGTTTTCAAAACACATAGTTA

Figure 41

GAATTCGTTCAGCCTGGTTAAGTCCAAGCTGGCTCATTCTGCTCCCCCGGGTCGGAGCCCCCCG
GAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCGCGCTGTCCTCCCGGTGTCCCGCTTCTCCGCGC
CCCAGCCGCCGGCTGCCAGCTTTTCGGGGCCCCGAGTCGCACCCAGCGAAGAGAGCGGGCCCG
GGACAAGCTCGAACTCCGGCCGCCTCGCCCTTAACCAGCTCCGTCCCTCTACCCCCTAGGGGTC
GCGCCCACGATGCTGCAGGGCCCTGGCTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCT
GGGCTCGGCGCGCGGGCTCTTCCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGC
AAGCCCATCCCGGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCC
AACCTGCTGGGCCACGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTG
GTCATGAAGCAGTGCCACCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCC
TCGATGACCTAGACGAGACCATCCAGCCATGCCACTCTCGNTGCGTGCAGGTGAAGGATCGCT
GCGCCCCGGTCATGTCCGCCTTCCCCTGGCCCGACATGCTTGAGTGCGACCGTTTCCCCCAGGA
CAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGAGGAAGCTCCA
AAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAACGACATAATGGAAACGCTTTGT
AAAAATGATTTTGCACTGAAAATAAAAGTGAAGGAGATAACCTACATCAACCGT

Figure 42

CCGGGTCGGAGCCCCCCGGAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCGCGCTGTCCTCCCGGTGTCCC
GCTTCTCCGCGCCCCAGCCGCCGGCTGCCAGCTTTTCGGGGCCCCGAGTCGCACCCAGCGAAGAGAGCGG
GCCCGGGACAAGCTCGAACTCCGGCCGCCTCGCCCTTCCCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTC
GCGCGCCCACGATGCTGCAGGGCCCTGGCTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGG
CTCGGCGCGCGGGCTCTTCCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATC
CCTGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCCAACCTGCTGGGCCACG
AGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTGGTCATGAAGCAGTGCCACCCGGA
CACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGACCTAGACGAGACCATCCAGCCA
TGCCACTCGCTCTGCGTGCAGGTGAAGGACCGCTGCGCCCCGGTCATGTCCGCCTTCGGCTTCCCCTGGC
CCGACATGCTTGAGTGCGACCGTTTCCCCCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCA
CCTCCTGCCAGCCACCGAGGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAAC
GACATAATGGAAACGCTTTGTAAAAATGATTTTGCACTGAAAATAAAAGTGAAGGAGATAACCTACATCA
ACCGAGATACCAAAATCATCCTGGAGACCAAGAGCAAGACCATTTACAAGCTGAACGGTGTGTCCGAAAG
GGACCTGAAGAAATCGGTGCTGTGGCTCAAAGACAGCTTGCAGTGCACCTGTGAGGAGATGAACGACATC
AACGCGCCCTATCTGGTCATGGGACAGAAACAGGGTGGGGAGCTGGTGATCACCTCGGTGAAGCGGTGGC
AGAAGGGGCAGAGAGAGTTCAAGCGCATCTCCCGCAGCATCCGCAAGCTGCAGTGCTAGTCCCGGCATCC
TGATGGCTCCGACAGGCCTGCTCCAGAGCACGGCTGACCATTTCTGCTCCGGGATCTCAGCTCCCGTTCC
CCAAGCACACTCCTAGCTGCTCCAGTCTCAGCCTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCATCC
CCAGCATTTCCTGAGTTATAAGGCCACAGGAGTGGATAGCTGTTTTCACCTAAAGGAAAAGCCCACCCGA
ATCTTGTAGAAATATTCAAACTAATAAAATCATGAATATTTTTATGAAGTTT

Figure 43

ACGGGGCCTGGGCGGSAGGGGCGGTGGCTGGAGCTCGGTAAAGCTCGTGGACCCCATTGGGG
GAATTTGATCCAAGGAAGCGGTGATTGCCGGGGGAGGAGAAGCTCCCAGATCCTTGTGTCCAC
TTGCAGCGGGGGAGGCGGAGACGCGGAGCGGGCCTTTTGGCGTCCACTGCGCGGCTGCACCCT
GCCCCATCCTGCCGGGATCATGGTCTGCGGCAGCCCGGGAGGGATGCTGCTGCTGCGGGCCGG
GCTGCTTGCCCTGGCTGCTCTCTGCCTGCTCCGGGTGCCCGGGGCTCGGGCTGCAGCCTGTGAG
CCCGTCCGCATCCCCCTGTGCAAGTCCCTGCCCTGGAACATGACTAAGATGCCCAACCACCTGC
ACCACAGCACTCAGGCCAACGCCATCCTGGCCATCGAGCAGTTCGAAGGTCTGCTGGGCACCC
ACTGCAGCCCCGATCTGCTCTTCTTCCTCTGTGCCATGTACGCGCCCATCTGCACCATTGACTTC
CAGCACGAGCCCATCAACCCCTGTAAGTCTGTGTGCGAGCGGGCCCGGCAGGGCTGTGAGCCC
ATACTCATCAAGTACCGCCACTCGTGGCCGGAGAACCTGGCCTGCGAGGAGCTGCCAGTGTAC
GACAGGGGCGTGTGCATCTCTCCCGAGGCCATCGTTACTGCGGACGGAGCTGATTTTCCTATGG
ATTCTAGTAACGGAAACTGTAGAGGGGCAAGCAGTGAACGCTGTAAATGTAAGCCTATTAGAG
CTACACAGAAGACCTATTTCCGGAACAATTACAACTATGTCATTCGGGCTAAAGTTAAAGAGAT
AAAGACTAAGTGCCATGATGTGACTGCAGTAGTGGAGGTGAAGGAGATTCTAAAGTCCTCTCT
GGTAAACATTCCACGGGACACTGTCAACCTCTATACCAGCTCTGGCTGCCTCTGCCCTCCACTT
AATGTTAATGAGGAATATATCATCATGGGCTATGAAGATGAGGAACGTTCCAGATTACTCTTGG
TGGAAGGCTCTATAGCTGAGAAGTGGAAGGATCGACTCGGTAAAAAAGTTAAGCGCTGGGATA
TGAAGCTTCGTCATCTTGGACTCAGTAAAAGTGATTCTAGCAATAGTGATTCCACTCAGAGTCA
GAAGTCTGGCAGGAACTCGAACCCCCGGCAAGCACGCAACTAAATCCCGAAATACAAAAAGTA
ACACAGTGGACTTCCTATTAAGACTTACTTGCATTGCTGGACTAGCAAAGGAAAATTGCACTAT
TGCACATCATATTCTATTGTTTACTATAAAAATCATGTGATAACTGATTATTACTTCTGTTTCTCT
TTTGGTTTCTGCTTCTCTCTTCTCTCAACCCCTTTGTAATGGTTTGGGGGCAGACTCTTAAGTATA
TTGTGAGTTTTCTATTTCACTAATCATGAGAAAAACTGTTCTTTTGCAATAATAATAAATTAAAC
ATGCTGTTA

Figure 44

CAGCGGCCGCTGAATTCTAGGGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTG
CCCTGTGTGCCAGACGGCGGAGCTCCGCGGCCGGACCCCGCGGCCCCGCTTTGCTGCCGACTGG
AGTTTGGGGGAAGAAACTCTCCTGCGCCCCAGAAGATTTCTTCCTCGGCGAAGGGACAGCGAA
AGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGGGGTCGCAGCGCGAGAGGGCA
GTGCCATGTTCCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACCTGGCGCTGGGCGTGCG
CGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGGAACATCACGCG
GATGCCCAACCACCTGCACCACAGCACGCAGGAGAACGCCATCCTGGCCATCGAGCAGTACGA
GGAGCTGGTGGACGTGAACTGCAGCGCCGTGCTGCGCTTCTTCTTCTGTGCCATGTACGCGCCC
ATTTGCACCCTGGAGTTCCTGCACGACCCTATCAAGCCGTGCAAGTCGGTGTGCCAACGCGCGC
GCGACGACTGCGAGCCCCTCATGAAGATGTACAACCACAGCTGGCCCGAAAGCCTGGCCTGCG
ACGAGCTGCCTGTCTATGACCGTGGCGTGTGCATTTCGCCTGAAGCCATCGTCACGGACCTCCC
GGAGGATGTTAAGTGGATAGACATCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGT
TGACTGTAAACGCCTAAGCCCCGATCGGTGCAAGTGTAAAAAGGTGAAGCCAACTTTGGCAAC
GTATCTCAGCAAAAACTACAGCTATGTTATTCATGCCAAAATAAAAGCTGTGCAGAGGAGTGG
CTGCAATGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCAAGTCCTCATCACCCATCCCT
CGAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACATCCTGCCCCATCAAG
ATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGGATGATGCTTCTTGAAAATTGCTTAGTTGAA
AAATGGAGAGATCAGCTTAGTAAAAGATCCATACAGTGGGAAGAGAGGCTGCAGGAACAGCG
GAGAACAGTTCAGGACAAGAAGAAAACAGCCGGGCGCACCAGTCGTAGTAATCCCCCCAAACC
AAAGGGAAAGCCTCCTGCTCCCAAACCAGCCAGTCCCAAGAAGAACATTAAAACTAGGAGTGC
CCAGAAGAGAACAAACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGAC
TTCCTTACAGGATGAGGCTGGGCATTGCCTGGGACAGCCTATGTAAGGCCATGTGCCCCTTGCC
CTAACAACTCACTGCAGTGCTCTTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTATGCTTC
AGTTTTTCTTTGTAAGCCATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACAGAAGGTGAG
TTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTCAGAGTAACCTGTGTGCATACTCTAGAAG
AGTAGGGAAAATAATGCTTGTTACAATTCGACCTAATATGTGCATTGTAAAATAAATGCCATAT
TTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTATTACCTTTTGATATCTGTTGTTGCAAT
GTTAGTGATGTTTTAAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGTAGTGGAATGA
ATGTTAAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTTGTGATGAAAGGGGATTTTTT

GAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTTTTTACCAATGACTTCAGTTTC
TGTTTTTAGCTAGAAACTTAAAAACAAAAATAATAATAAAGAAAAATAAATAAAAAGGAGAGG
CAGACAATGTCTGGATTCCTGTTTTTGGTTACCTGATTTCCATGATCATGATGCTTCTTGTCAA
CACCCTCTTAAGCAGCACCAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATT
AGTTGGCTAATGCTCAAGTATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCCAG
GACATCCACCCTGAGAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTG
TTTTTCTTCATTTAAATATTTTCTTTGCCTAAATACATGTGAGAGGAGTTAAATATAAATGTACA
GAGAGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGACAGTTGGGATACTTTAATCAG
AAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTCATAATTGTGGACAATTGGAGGCAT
TTATTTTAAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCATGTATTTTATAAGGCATT
CAATAAATGCACAACGCCCAAAGGAAATAAAATCCTATCTAATCCTACTCTCCACTACACAGA
GGTAATCACTATTAGTATTTTGGCATATTATTCTCCAGGTGTTTGCTTATGCACTTATAAAATGA
TTTGAACAAATAAAACTAGGAACCTGTATACATGTGTTTCATAACCTGCCTCCTTTGCTTGGCCC
TTTATTGAGATAAGTTTTCCTGTCAAGAAAGCAGAAACCATCTCATTTCTAACAGCTGTGTTATA
TTCCATAGTATGCATTACTCAACAAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGA
CAATACTGAATAAACATCTCACCGGAATTC

Figure 45

AAGCTTGATATCGAATTCGCGGCCGCGTCGACGGAGGCGCCAGGATCAGTCGGGGCACCCGC
AGCGCAGGCTGCCACCCACCTGGGCGACCTCCGCGGCGGCGGCGGCGGCGGCTGGGTAGAGTC
AGGGCCGGGGGCGCACGCCGGAACACCTGGGCCGCCGGGCACCGAGCGTCGGGGGGCTGCGC
GGCGCGACCCTGGAGAGGGCGCAGCCGATGCGGGCGGCGGCGGCGGCGGGGGGCGTGCGGAC
GGCCGCGCTGGCGCTGCTGCTGGGGGCGCTGCACTGGGCGCCGGCGCGCTGCGAGGAGTACGA
CTACTATGGCTGGCAGGCCGAGCCGCTGCACGGCCGCTCCTACTCCAAGCCGCCGCAGTGCCTT
GACATCCCTGCCGACCTGCCGCTCTGCCACACGGTGGGCTACAAGCGCATGCGGCTGCCCAACC
TGCTGGAGCACGAGAGCCTGGCCGAAGTGAAGCAGCAGGCGAGCAGCTGGCTGCCGCTGCTGG
CCAAGCGCTGCCACTCGGATACGCAGGTCTTCCTGTGCTCGCTCTTTGCGCCCGTCTGTCTCGAC
CGGCCCATCTACCCGTGCCGCTCGCTGTGCGAGGCCGTGCGCGCCGGCTGCGCGCCGCTCATGG
AGGCCTACGGCTTCCCCTGGCCTGAGATGCTGCACTGCCACAAGTTCCCCCTGGACAACGACCT
CTGCATCGCCGTGCAGTTCGGGCACCTGCCCGCCACCGCGCCTCCAGTGACCAAGATCTGCGCC
CAGTGTGAGATGGAGCACAGTGCTGACGGCCTCATGGAGCAGATGTGCTCCAGTGACTTTGTG
GTCAAAATGCGCATCAAGGAGATCAAGATAGAGAATGGGGACCGGAAGCTGATTGGAGCCCA
GAAAAAGAAGAAGCTGCTCAAGCCGGGCCCCCTGAAGCGCAAGGACACCAAGCGGCTGGTGC
TGCACATGAAGAATGGCGCGGGCTGCCCCTGCCCACAGCTGGACAGCCTGGCGGGCAGCTTCC
TGGTCATGGGCCGCAAAGTGGATGGACAGCTGCTGCTCATGGCCGTCTACCGCTGGGACAAGA
AGAATAAGGAGATGAAGTTTGCAGTCAAATTCATGTTCTCCTACCCCTGCTCCCTCTACTACCCT
TTCTTCTACGGGGCGGCAGAGCCCCACTGAAGGGCACTCCTCCTTGCCCTGCCAGCTGTGCCTT
GCTTGCCCTCTGGCCCCGCCCCAACTTCCAGGCTGACCCGGCCCTACTGGAGGGTGTTTTCACG
AATGTTGTTACTGGCACAAGGCCTAAGGGATGGCACGGAGCCCAGGCTGTCCTTTTTGACCCA
GGGGTCCTGGGGTCCCTGGGATGTTGGGCTTCCTCTCTCAGGAGCAGGGCTTCTTCATCTGGGT
GAAGACCTCAGGGTCTCAGAAAGTAGGCAGGGGAGGAGAGGGTAAGGGAAAGGTGGAGGGGC
TCAGGGCACCCTGAGGCGGAGGTTTCAGAGTAGAAGGTGATGTCAGCTCCAGCTCCCCTCTGTC
GGTGGTGGGGCCTCACCTTGAAGAGGGAAGTCTCAATATTAGGCTAAGCTATTTGGGAAAGTTC
TCCCCACCGCCCCTGTACGCGTCATCCTAGCCCCCCTTAGGAAAGGAGTTAGGGTCTCAGTGCC
TCCAGCCACACCCCCTGCCTTCCCCAGCTTGCCCATTTCCCTGCCCCAAGGCCCAGAGCTCCCCC
CAGACTGGAGAGCAAGCCCAGCCCAGCCTCGGCATAGACCCCCTTCTGGTCCGCCCGTGGCTCG
ATTCCCGGGATTCATTCCTCAGCCTCTGCTTCTCCCTTTTATCCCAATAAGTTATTGCTACTGCTG
TGAGGCCATAGGTACTAGACAACCAATACATGCAGGGTTGGGTTTTCTAATTTTTTTAACTTTTT
AATTAAATCAAAGGTCGACGCGCGGCCGCGGAATTCCTGCAGCCCGGGGGATCCCCGGGTACC
GAGCTCGAATTC

Figure 46

ATGCATCTCCTCTTATTTCAGCTGCTGGTACTCCTGCCTCTAGGAAAGACCACACGGCACCAGG
ATGGCCGCCAGAATCAGAGTTCTCTTTCCCCCGTACTCCTGCCAAGGAATCAAAGAGAGCTTCC
CACAGGCAACCATGAGGAAGCTGAGGAGAAGCCAGATCTGTTTGTCGCAGTGCCACACCTTGT
AGCCACCAGCCCTGCAGGGGAAGGCCAGAGGCAGAGAGAGAAGATGCTGTCCAGATTTGGCA
GGTTCTGGAAGAAGCCTGAGAGAGAAATGCATCCATCCAGGGACTCAGATAGTGAGCCCTTCC
CACCTGGGACCCAGTCCCTCATCCAGCCGATAGATGGAATGAAAATGGAGAAATCTCCTCTTCG
GGAAGAAGCCAAGAAATTCTGGCACCACTTCATGTTCAGAAAAACTCCGGCTTCTCAGGGGGT
CATCTTGCCCATCAAAAGCCATGAAGTACATTGGGAGACCTGCAGGACAGTGCCCTTCAGCCA
GACTATAACCCACGAAGGCTGTGAAAAAGTAGTTGTTCAGAACAACCTTTGCTTTGGGAAATGC
GGGTCTGTTCATTTTCCTGGAGCCGCGCAGCACTCCCATACCTCCTGCTCTCACTGTTTGCCTGC
CAAGTTCACCACGATGCACTTGCCACTGAACTGCACTGAACTTTCCTCCGTGATCAAGGTGGTG
ATGCTGGTGGAGGAGTGCCAGTGCAAGGTGAAGACGGAGCATGAAGATGGACACATCCTACAT
GCTGGCTCCCAGGATTCCTTTATCCCAGGAGTTTCAGCTTGA

Figure 47

CGGCACGGTTTCGTGGGGACCCAGGCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCTCCCTCT
TGAGTCCTTCTGAGATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTTGTCGCGATGGT
AGCGGCGGCTCTCGGCGGCCACCCTCTGCTGGGAGTGAGCGCCACCTTGAACTCGGTTCTCAAT
TCCAACGCTATCAAGAACCTGCCCCCACCGCTGGGCGGCGCTGCGGGGCACCCAGGCTCTGCA
GTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGAATAAGTACCAGACCATTGACAACTAC
CAGCCGTACCCGTGCGCAGAGGACGAGGAGTGCGGCACTGATGAGTACTGCGCTAGTCCCACC
CGCGGAGGGGACGCAGGCGTGCAAATCTGTCTCGCCTGCAGGAAGCGCCGAAAACGCTGCATG
CGTCACGCTATGTGCTGCCCCGGGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAA
ATCATTTCCGAGGAGAAATTGAGGAAACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTT
GGATGGGTATTCCAGAAGAACCACCTTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGG
TTCTGTTTGTCTCCGGTCATCAGACTGTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCA
AGATCTGTAAACCTGTCCTGAAAGAAGGTCAAGTGTGTACCAAGCATAGGAGAAAAGGCTCTC
ATGGACTAGAAATATTCCAGCGTTGTTACTGTGGAGAAGGTCTGTCTTGCCGGATACAGAAAGA
TCACCATCAAGCCAGTAATTCTTCTAGGCTTCACACTTGTCAGAGACACTAAACCAGCTATCCA
AATGCAGTGAACTCCTTTTATATAATAGATGCTATGAAAACCTTTTATGACCTTCATCAACTCAA
TCCTAAGGATATACAAGTTCTGTGGTTTCAGTTAAGCATTCCAATAACACCTTCCAAAAACCTG
GAGTGTAAGAGCTTTGTTTCTTTATGGAACTCCCCTGTGATTGCAGTAAATTACTGTATTGTAAA
TTCTCAGTGTGGCACTTACCTGTAAATGCAATGAAACTTTTAATTATTTTTCTAAAGGTGCTGCA
CTGCCTATTTTTCCTCTTGTTATGTAAATTTTTGTACACATTGATTGTTATCTTGACTGACAAATA
TTCTATATTGAACTGAAGTAAATCATTTCAGCTTATAGTTCTTAAAAGCATAACCCTTTACCCCA
TTTAATTCTAGAGTCTAGAACGCAAGGATCTCTTGGAATGACAAATGATAGGTACCTAAAATGT
AACATGAAAATACTAGCTTATTTCTGAAATGTACTATCTTAATGCTTAAATTATATTTCCCTTT
AGGCTGTGATAGTTTTTGAAATAAAATTTAACATTTAATATCATGAAATGTTATAAGTAGACAT

Figure 48

GCGGGTCTCGCTTGGGTTCCGCTAATTTCTGTCCTGAGGCGTGAGACTGAGTTCATAGGGTCCT
GGGTCCCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGCGACCCAAGTGAGG
GGCCCCGTGTTGGGGTCCTCCCTCCCTTTGCATTCCCACCCCTCCGGGCTTTGCGTCTTCCTGGG
GACCCCCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGGATTCGTCCTGCTGCCTGCTCCT
ACTGGCCGCGGTGCTGATGGTGGAGAGCTCACAGATCGGCAGTTCGCGGGCCAAACTCAACTC
CATCAAGTCCTCTCTGGGCGGGGAGACGCCTGGTCAGGCCGCCAATCGATCTGCGGGCATGTAC
CAAGGACTGGCATTCGGCGGCAGTAAGAAGGGCAAAAACCTGGGGCAGGCCTACCCTTGTAGC
AGTGATAAGGAGTGTGAAGTTGGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGC
ATGGTGTGTCGGAGAAAAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGC
TGCAATAATGGCATCTGTATCCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGG
ATGGTACTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGA
ATCTAGGAAGACCACACACTAAGATGTCACATATAAAAGGGCATGAAGGAGACCCCTGCCTAC
GATCATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCAAAATCTGCAAACC

AGTGCTCCATCAGGGGGAAGTCTGTACCAAACAACGCAAGAAGGGTTCTCATGGCTGGAAAT
TTTCCAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATGGAAAGATGCCACCTACTCC
TCCAAAGCCAGACTCCATGTGTGTCAGAAAATTTGATCACCATTGAGGAACATCATCAATTGCA
GACTGTGAAGTTGTGTATTTAATGCATTATAGCATGGTGGAAAATAAGGTTCAGATGCAGAAG
AATGGCTAAAATAAGAAACGTGATAAGAATATAGATGATCAC

Figure 49

CTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCACCGAGA
AATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAGTTATCACATCT
GTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCCAG
CATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTC
TGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATG
GCCACCAGGGGCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGC
TGTGCCTTCCAGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTT
GCCATGACCCCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTT
GGACCGATGCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTG
TGCAAGCCGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTC
CCCGATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAG
AGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGA
GGGGAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTAT
TTCCCCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTACATCTTCTTCCCAGTAAG
TTTCCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTCAGCTCCCCCAGGCTGTTCTCCA
GGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACC
CCTGTCCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTTCTACATGGCT
TTGATAATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGGG
AAATGTGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATT
TTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTTC
TGTTCACCCTGCATTACATGTGTTTATTCATCCAGCAGTGTTGCTCAGCTCCTACCTCTGTGCCA
GGGCAGCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCACAGCCTGGGGAGGGGGTCATTG
TTCTCCTCGTCCATCAGGGATCTCAGAGGNCTCAGAGACTGCAAGCTGCTTGCCCAAGTCACAC
AGCTAGTGAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTAC
CCCACACCAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTT
TGAGGCATGCACATCTGGAATTAAGGTCAAACTAATTCTCACATCCCTCTAAAAGTAAACTACT
GTTAGGAACAGCAGTGTTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTG
ACACTGTCCCTCTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATAC
AGGTTAACCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCA
AAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGG
CTGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAATGA
TGTTTTCAGGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAAAGTTTAAAGTTG
CACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACATAAGTTGCATTTAG
AAATCAAGCATAAATCAC

Figure 50

AGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGCCTCGCTTT
GGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTGGCGGCCGTCCT
GCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGGTCCTGGACTTCAACAACATCAGG
AGCTCTGCTGACCTGCATGGGGCCCGGAAGGGCTCACAGTGCCTGTCTGACACGGACTGCAAT
ACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGCCGTTCTGTGCTACATGTCGTGGGTTGC
GGAGGAGGTGCCAGCGAGATGCCATGTGCTGCCCTGGGACACTCTGTGTGAACGATGTTTGTAC
TACGATGGAAGATGCAACCCCAATATTAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGC
AGAAGGAACAACTGGGCACCCAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGA
AATCACAAGGCAGGAAGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTGACTGTGGCCCTG

GACTTTGCTGTGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAGGT
CTGCTCCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTTGCGACTGT
GGCCCTGGACTACTGTGTCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGATTAAGAGTAT
GCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAATCCACATTGC

Figure 51

AGGCAGAATACTTCTATGAATTCCTGTCCTTGCGCTCCCTGGATAAAGGCATCATGGCAGATCC
AACCGTCAATGTCCCTCTGCTGGGAACAGTGCCTCACAAGGCATCAGTTGTTCAAGTTGGTTTC
CCATGTCTTGGAAAACAGGATGGGGTGGCAGCATTTGAAGTGGATGTGATTGTTATGAATTCTG
AAGGCAACACCATTCTCCAAACACCTCAAAATGCTATCTTCTTTAAAACATGTCAACAAGCTGA
GTGCCCAGGCGGGTGCCGAAATGGAGGCTTTTGTAATGAAAGACGCATCTGCGAGTGTCCTGA
TGGGTTCCACGGACCTCACTGTGAGAAAGCCCTTTGTACCCCACGATGTATGAATGGTGGACTT
TGTGTGACTCCTGGTTTCTGCATCTGCCCACCTGGATTCTATGGAGTGAACTGTGACAAAGCAA
ACTGCTCAACCACCTGCTTTAATGGAGGGACCTGTTTCTACCCTGGAAAATGTATTTGCCCTCCA
GGACTAGAGGGAGAGCAGTGTGAAATCAGCAAATGCCCACAACCCTGTCGAAATGGAGGTAA
ATGCATTGGTAAAAGCAAATGTAAGTGTTCCAAAGGTTACCAGGGAGACCTCTGTTCAAAGCCT
GTCTGCGAGCCTGGCTGTGGTGCACATGGAACCTGCCATGAACCCAACAAATGCCAATGTCAA
GAAGGTTGGCATGGAAGACACTGCAATAAAAGGTACGAAGCCAGCCTCATACATGCCCTGAGC
GCAGCAGCGCCCAGCTCAGGCAGCACACGCCTTCACTTAAAAAGGCCGAGGAGCGGCGGCATC
CACCTGAATCCAATTACATCTGGTGAACTCCGACATCTGAAACGTTTTAAGTTACACCAAGTTC
ATAGCCTTTGTTAACCTTTCATGTGTTGAATGTTCAAATAATGTTCATTACACTTAAGAATACTG
GCCTGAATTTTATTAGCTTCATTATAAATCACTGAGCTGATATTTACTCTTCCTTTTAAGTTTTCT
AAGTACGTCTGTAGCATGATGGTATAGATTTTCTTGTTTCAGTGCTTTGGGACAGATTTTATATT
ATGTCAATTGATCAGGTTAAAATTTTCAGTGTGTAGTTGGCAGATATTTTCAAAATTACAATGC
ATTTATGGTGTCTGGGGGCAGGGGAACATCAGAAAGGTTAAATTGGGCAAAAATGCGTAAGTC
ACAAGAATTTGGATGGTGCAGTTAATGTTGAAGTTACAGCATTTCAGATTTTATTGTCAGATAT
TTAGATGTTTGTTACATTTTTAAAAATTGCTCTTAATTTTTAAACTCTCAATACAATATATTTTGA
CCTTACCATTATTCCAGAGATTCAGTATTAAAAAAAAAAAAATTACACTGTGGTAGTGGCATTT
AAACAATATAATATATTCTAAACACAATGAAATAGGGAATATAATGTATGAACTTTTTGCATTG
GCTTGAAGCAATATAATATATTGTAAACAAAACACAGCTCTTACCTAATAAACATTTTATACTG
TTTGTATGTATAAAATAAAGGTGCTGCTTTAGTTTTC

Figure 52

ATGGGCATCGGGCGCAGCGAGGGGGGCCGCCGCGGGGCAGCCCTGGGCGTGCTGCTGGCGCTGGGCGCGG
CGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCTTCCAGTCGGACATCGGCCCGTACCA
GAGCGGGCGCTTCTACACCAAGCCACCTCAGTGCGTGGACATCCCCGCGGACCTGCGGCTGTGCCACAAC
GTGGGCTACAAGAAGATGGTGCTGCCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCAGG
CCAGCAGCTGGGTGCCCCTGCTCAACAAGAACTGCCACGCCGGCACCCAGGTCTTCCTCTGCTCGCTCTT
CGCGCCCGTCTGCCTGGACCGGCCCATCTACCCGTGTCGCTGGCTCTGCGAGGCCGTGCGCGACTCGTGC
GAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGCCCGAGATGCTTAAGTGTGACAAGTTCCCCGAGGGGG
ACGTCTGCATCGCCATGACGCCGCCCAATGCCACCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCC
TCCCTGTGACAACGAGTTGAAATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGGGCTGAGT
TTAAAGATGATTGTGGGTAGCTCCCATAACTCATGCTGCACGCTGGGTCCTTCTCATCCCAACTCCTCAA
AGCGGCAGGAGCAGGAACTGGGGACTCCTGAGAGAAGGCTTGGATATGGCCTTTTATTACACTTCATCCA
AGGAAATCTGCCCCCACCCTGTGCCCAGGCCCGATCACGCATGAGGCTAAAGACGGAGGCCACTCCGCTG
GCTCTGGGTAGATCTGCCCCTGGACTGTTTGCCGACTGCCCGGAGCGCCCTCTGCCGGTCTGCAGCTTCC
CACACCACACGGAAGAAGTGGGGAAACTGAGGATACATTCTTTCCTCCTCCAGGTAAAGGGATTCTCAAT
GAAGGGCTTGTGTGCACCTTCCACACTTAGATACCTCTACTACCTGAAAACCAGCATGCAGCATGTACAT
CAAGAGTACCAGGCACATAGTGCTCAAGTCTGGGCTAATATGCCACCTGCAGAGAGATGTAAAGATGAAG
AAGACAAAGCCATGTTTTCAAAGTGA

Figure 53

GGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTGCCCTGTGTGCCAGACGGCGGAGCTCCG
CGGCCGGACCCCGCGGCCCCGCTTTGCTGCCGACTGGAGTTTGGGGGAAGAAACTCTCCTGCGCCCCAGA
AGATTTCTTCCTCGGCGAAGGGACAGCGAAAGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCC
GGGGTCGCAGCGCGAGAGGGCAGTGCCATGTTCCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACC
TGGCGCTGGGCGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGGAA
CATCACGCGGATGCCCAACCACCTGCACCACAGCACGCAGGAGAACGCCATCCTGGCCATCGAGCAGTAC
GAGGAGCTGGTGGACGTGAACTGCAGCGCCGTGCTGCGCTTCTTCTTCTGTGCCATGTACGCGCCCATTT
GCACCCTGGAGTTCCTGCACGACCCTATCAAGCCGTGCAAGTCGGTGTGCCAACGCGCGCGCGACGACTG
CGAGCCCCTCATGAAGATGTACAACCACAGCTGGCCCGAAAGCCTGGCCTGCGACGAGCTGCCTGTCTAT
GACCGTGGCGTGTGCATTTCGCCTGAAGCCATCGTCACGGACCTCCCGGAGGATGTTAAGTGGATAGACA
TCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGTTGACTGTAAACGCCTAAGCCCCGATCGGTG
CAAGTGTAAAAAGGTGAAGCCAACTTTGGCAACGTATCTCAGCAAAAACTACAGCTATGTTATTCATGCC
AAAATAAAAGCTGTGCAGAGGAGTGGCTGCAATGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCA
AGTCCTCATCACCCATCCCTCGAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACAT
CCTGCCCCATCAAGATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGGATGATGCTTCTTGAAAATTGC
TTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGATCCATACAGTGGGAAGAGAGGCTGCAGGAACAGC
GGAGAACAGTTCAGGACAAGAAGAAAACAGCCGGGCGCACCAGTCGTAGTAATCCCCCCAAACCAAAGGG
AAAGCCTCCTGCTCCCAAACCAGCCAGTCCCAAGAAGAACATTAAAACTAGGAGTGCCCAGAAGAGAACA
AACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTACAGGATGAGGCTG
GGCATTGCCTGGGACAGCCTATGTAAGGCCATGTGCCCCTTGCCCTAACAACTCACTGCAGTGCTCTTCA
TAGACACATCTTGCAGCATTTTTCTTAAGGCTATGCTTCAGTTTTTCTTTGTAAGCCATCACAAGCCATA
GTGGTAGGTTTGCCCTTTGGTACAGAAGGTGAGTTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTCA
GAGTAACCTGTGTGCATACTCTAGAAGAGTAGGGAAAATAATGCTTGTTACAATTCGACCTAATATGTGC
ATTGTAAAATAAATGCCATATTTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTATTACCTTTTGA
TATCTGTTGTTGCAATGTTAGTGATGTTTTAAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGT
AGTGGAATGAATGTTAAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTTGTGATGAAAGGGGAT
TTTTTGAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTTTTTTACCAATGACTTCAGTTTCT
GTTTTTAGCTAGAAACTTAAAAACAAAAATAATAATAAAGAAAAATAAATAAAAAGGAGAGGCAGACAAT
GTCTGGATTCCTGTTTTTTGGTTACCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCTCTTAAGC
AGCACCAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTAGTTGGCTAATGCTCAAGT
ATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCCAGGACATCCACCCTGAGAATAATTTGA
CAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTGTTTTTCTTCATTTAAATATTTTCTTTGCCTA
AATACATGTGAGAGGAGTTAAATATAAATGTACAGAGAGGAAAGTTGAGTTCCACCTCTGAAATGAGAAT
TACTTGACAGTTGGGATACTTTAATCAGAAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTCAT
AATTGTGGACAATTGGAGGCATTTATTTTAAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCAT
GTATTTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAATAAAATCCTATCTAATCCTACTCTCC
ACTACACAGAGGTAATCACTATTAGTATTTTGGCATATTATTCTCCAGGTGTTTGCTTATGCACTTATAA
AATGATTTGAACAAATAAAACTAGGAACCTGTATACATGTGTTTCATAACCTGCCTCCTTTGCTTGGCCC
TTTATTGAGATAAGTTTTCCTGTCAAGAAAGCAGAAACCATCTCATTTCTAACAGCTGTGTTATATTCCA
TAGTATGCATTACTCAACAAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGACAATACTGAA
TAAACATCTCACCGGAATTC

Figure 54

GAGGCGCCTTGGGACCGCGTGGGAGCCGCAGCCGAACCGAGTAGGGACCGGGACCGCGCGGCGCCGCCG
TCCCCGGCCGGGCCCGGCCCCCGCGAGCCGAGCGCGCGCCCCCGTCGCCCACCCGGGCGCGGCTGGATGC
GGCGGGGTCCCCGCGGCGGCGACCCCCGGCCCCGAGCGCCCGGAGCGCCCAGAGGCGGCGTGCGGGGCC
CGGGGACGCCGCGCCCTSTBGTGCGCCGAGGCGCGCCCCGAGACAGCCGGGGGCCCGCGCCGCAGCCGC
CGCCCGCGCTGAGCCCCGGCCCGGCCCGCGGCCCGCGCCCGGCGGCAGCNTGAGCCAGGCCGAGCTGTC
CACCTGCTCCGCGCCGCAGACGCAGCGCATCTTCCAGGAGGCTGTGCGCNAGGGCAACACGCAGGAGCT
GCAGTYGCTGCTGCAGAACATGACCAACTGCGAGTTCAACGTGAACTCGTTCGGGCCCGAGGGCCAGAC
GGCGCTGCACCAGTCGGTCATCGTCGGCAACCTGGTGCTCGTGAAGCTGCTGGTCAAGTTCGGCGCCGAC
ATCCGCCTGGCCAACCGCGACGGCTGGAGCGCGCTGCAMATCGCCGCGTTCGGTGGCCACCAGGACATC
GTGCTCTATCTCATCACCAAGGCGAAGTACGCGGCCAGCGCSGGTGTATGCCCGCCGGGACCCCGGACCC
CGGCCCTGCGCCCGCGTCGTCTCTGCTGTACCTTCCCGCCAACTACCTCGGTGCGCGCMCGGCTCGCAGG
CCCCGCCAGAAGGCCCGTGGCAACGGCGAATACGGCGCGTGCGTCMCGGCCCCAGGGTC

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: METHOD FOR MODULATING STEM CELL DIFFERENTIATION USING STEM LOOP RNA

(57) Abstract: This invention relates to a method to promote the differentiation of stem cells, typically embryonic stem cells, through the use of RNA interference, by the introduction of stem loop RNA into a cell.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03409

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/06 C12N15/11 A61K48/00 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 03743 A (GEHRING WALTER; ARTAVANIS TSAKONAS SPYRIDON) 18 January 2001 (2001-01-18) page 39 -page 45 page 52 -page 60 ---	1-5, 7-22, 25-27, 30,33
Y	WO 01 36646 A (CANCER RES CAMPAIGN TECHN LIM (GB) ZERNICKA-GOETZ WIANNY EVANS GLOVER) 25 May 2001 (2001-05-25) page 6, line 29 -page 7, line 12 page 11, line 28 page 20, line 21 -page 21, line 26 --- -/--	1-5, 7-22, 25-28, 30,33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2003	12. 08. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Macchia, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03409

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 25422 A (AVI BIOPHARMA, INC. (US); BARTELMEZ STEPHEN H.; IVERSEN PATRICK L.) 12 April 2001 (2001-04-12) page 4 page 16 -page 17	1-5, 7-22, 25-28, 30,33
P,X	WO 02 16620 A (UNIVERSITY OF SHEFFIELD (GB); ANDREWS PETER; WALSH JAMES; GOKHALE PAUL) 28 February 2002 (2002-02-28) the whole document	1,4-8, 12-23, 25-32
A	WO 98 58958 A (WASHINGTON UNIV PHILADELPHIA CHILDREN'S HOSPITAL; LI HOOD KRANTZ SPINN) 30 December 1998 (1998-12-30)	
A	WO 97 45143 A (NATL US RED CROSS; UNIV GENEVE; ZIMRIN; MACIAG; PEPPER; MONTESANO WONG) 4 December 1997 (1997-12-04) page 9, line 14-25 page 15, line 30 -page 36, line 4	
A	WO 00 25809 A (SMITH & NEPHEW PLC (GB); SKERRY T.M.; DALLAS D.J.; WOLOWACZ R.G.) 11 May 2000 (2000-05-11) the whole document	
A	WO 99 32619 A (CARNEGIE INST WASHINGTON; FIRE XU MONTGOMERY KOSTAS TIMMONS TABARA ET) 1 July 1999 (1999-07-01) page 10, line 28 -page 11, line 13 page 13, line 1-29 page 14, line 26-30 page 16, line 23	8-23,26, 27,32,33
A	WO 00 63364 A (AMERICAN HOME PRODUCTS CORPORATION; PACHUK CATHERINE SATISHCHANDRAN C.) 26 October 2000 (2000-10-26)	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/03409

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 and 25 (for claims 1-7, insofar as in vivo methods are concerned) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-6, 8-16, 18-33 all in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-33 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03409

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 25422 A (AVI BIOPHARMA, INC. (US); BARTELMEZ STEPHEN H.; IVERSEN PATRICK L.) 12 April 2001 (2001-04-12) page 4 page 16 -page 17	1-5, 7-22, 25-28, 30,33
P,X	WO 02 16620 A (UNIVERSITY OF SHEFFIELD (GB); ANDREWS PETER; WALSH JAMES; GOKHALE PAUL) 28 February 2002 (2002-02-28) the whole document	1,4-8, 12-23, 25-32
A	WO 98 58958 A (WASHINGTON UNIV PHILADELPHIA CHILDREN'S HOSPITAL; LI HOOD KRANTZ SPINN) 30 December 1998 (1998-12-30)	
A	WO 97 45143 A (NATL US RED CROSS; UNIV GENEVE; ZIMRIN; MACIAG; PEPPER; MONTESANO WONG) 4 December 1997 (1997-12-04) page 9, line 14-25 page 15, line 30 -page 36, line 4	
A	WO 00 25809 A (SMITH & NEPHEW PLC (GB); SKERRY T.M.; DALLAS D.J.; WOLOWACZ R.G.) 11 May 2000 (2000-05-11) the whole document	
A	WO 99 32619 A (CARNEGIE INST WASHINGTON; FIRE XU MONTGOMERY KOSTAS TIMMONS TABARA ET) 1 July 1999 (1999-07-01) page 10, line 28 -page 11, line 13 page 13, line 1-29 page 14, line 26-30 page 16, line 23	8-23,26, 27,32,33
A	WO 00 63364 A (AMERICAN HOME PRODUCTS CORPORATION; PACHUK CATHERINE SATISHCHANDRAN C.) 26 October 2000 (2000-10-26)	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/03409

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 and 25 (for claims 1-7, insofar as in vivo methods are concerned) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-6, 8-16, 18-33 all in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-33 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.